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c — correspondence
 cr — case record
 e — editorial

MMS — Massachusetts Medical Society
 mp — medical progress
 me — medical eponym

mr — meeting report
 misc — miscellany
 n — notice

o — obituary
 * — original article

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HODGKIN'S DISEASE*

I. General Considerations

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BOSTON

IT IS the purpose of this and the succeeding articles to give a brief account of the clinical picture of Hodgkin's disease, its treatment and its prognosis, together with such descriptions of the pathology of the condition in its various forms as seem necessary for an understanding of the limits of the entity included under this title. The study is based largely on material collected over a period of years from the Boston City Hospital, the Collis P. Huntington Memorial Hospital, the Pondville Hospital (Massachusetts Department of Public Health) and our private practice. From the Children's Hospital we have added certain data with the permission of Dr. W. E. Ladd.

No attempt will be made to cover exhaustively the extensive and often confusing literature. For a more complete bibliography, the reader is referred to the admirable review of Wallhauser¹ and the later work of Sternberg.²

CLASSIFICATION

In our opinion, Hodgkin's disease can and should be divided into three types—paragranuloma, granuloma and sarcoma.³ We believe that it is essential to recognize the existence of these three forms of the disease, for the pathologic picture, the clinical aspects and the prognosis differ materially with each. We hope to be able to show that this subdivision is of practical value to the clinician as well as to the pathologist. No originality is claimed for such a classification, but it is our belief that it is not so widely recognized and utilized as it should be.

The Germans include in their *Granulomatose* the granulomatous form and also some cases that we classify as sarcomatous. Sternberg did not recognize the paragranuloma type and denied the existence of the sarcoma. Ewing,⁴ however, postulated

the occurrence of the latter arising from the granulomatous type.

It should become clear as this presentation of the pathologic and clinical features of the three types of the disease proceeds that any description that includes all three as a single form of the disease must, of necessity, be inaccurate and of little practical value.

Paragranuloma, granuloma and sarcoma are included as three different types of Hodgkin's disease on the basis of two features. The first is the presence in each of the so-called "Reed-Sternberg" cells. We believe strongly that the diagnosis of Hodgkin's disease cannot be made in their absence. Some authors describe what they term an early form of the disease, characterized by hyperplasia and hypertrophy of the reticulum and endothelial cells without the presence of Reed-Sternberg cells. In our opinion, such a diagnosis is not justified. The second feature is the transformation, with the passage of time, of one type of the disease into another. Thus, a patient may be stricken with what is proved by biopsy to be Hodgkin's paragranuloma, and months or even years later a second biopsy may reveal the presence of Hodgkin's granuloma. Similarly, a granuloma may become a sarcoma, or much more rarely the two forms are found coexisting in the same patient or, exceptionally, in the same node. It should be emphasized in this connection that we have never encountered what might be termed a reverse transformation—that is, a Hodgkin's sarcoma reverting to a granuloma, or a granuloma regressing to a paragranuloma. What we regard as the most benign form may and frequently does progress into the more malignant one. The reverse never occurs.

Historical Summary

Hodgkin's paragranuloma. Hodgkin's paragranuloma first appeared in the literature under the unfortunate name "early Hodgkin's."⁵ To be sure, this type is often early in the sense that it is, in

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many cases, a precursor of the more rapidly advancing granulomatous type, yet patients with Hodgkin's paraganuloma may live unembarrassed by their disease—if the pathologic picture does not change—for many years. One patient (L. C., S36-1256) is living and active thirty-eight years after the first proved lymph-node involvement, although the condition, as shown by multiple biopsies, is still present. The term "early" under such circumstances is hardly an apt one. Therefore the designation "paraganuloma" has been introduced, the prefix indicating "in close relation to." So far as we are aware, this exact designation has not been used elsewhere in the literature.

Hodgkin's granuloma. We confine the term "Hodgkin's granuloma" to the type familiar to all. There is probably no other disease to which so many different names have been applied. Wallhauser¹ in his excellent review mentions more than fifty terms that have appeared. Such a state of affairs renders a study of the literature, and particularly the older literature, extremely difficult and has unquestionably caused much confusion and misunderstanding in the minds of students of the disease. The multiplicity of terminology is undoubtedly due to a lack of knowledge of the true nature of the condition.

In 1865, Wilks⁵ suggested the name "Hodgkin's disease." In addition to this term, the most widely used and most generally accepted are lymphadenoma,⁶ malignant lymphoma,⁷ malignant granuloma,⁸ lymphogranuloma⁹ and scirrhus lymphoblastoma.¹⁰ The *Index Medicus* used the term "Hodgkin's disease," whereas the *Quarterly Cumulative Index* listed the disease under lymphogranuloma until 1941, when the term "Hodgkin's disease" was reinstated.

Few diseases have been given a clear-cut, comprehensive and definitive description by the investigator who first brought them to the attention of the medical profession. Hodgkin's granuloma is no exception to this rule. In 1832, Thomas Hodgkin¹¹ described 7 cases with generalized lymphadenopathy and splenomegaly and noted that "as far as could be ascertained from observation, or from what could be collected from the history of the cases, this enlargement of the glands appeared to be a primitive affection of those bodies, rather than the result of an irritation propagated to them from some ulcerated surface or other inflamed texture through the medium of their inferent vessels." Hodgkin was further arrested by the state of the spleen, which in all but one case was found more or less diseased and in some cases was "thickly pervaded with defined bodies of various sizes in structure resembling that of the diseased glands." He concluded that there was "a close connection between the derangement of the glands and that of the spleen," and he believed that the latter was "a posterior effect and on this account may not

always have been produced, when that of the glands or some other disease carried off the patient."

It is true that among Hodgkin's original cases there were probably but 3, at most 4, of the condition that now bears his name,¹² and it has been the custom, from time to time, to belittle his contribution as uninspired and uninspiring. It would seem juster to acknowledge that the nineteenth-century physician recognized a disease entity at a time when pathology was in its infancy and when the microscopic examination of tissues was virtually unknown.

Hodgkin's contribution seemed, nevertheless, to have been lost sight of until 1856, when Sir Samuel Wilks¹³ described a number of cases of "lardaceous disease." He wrote with chivalrous honesty that on the completion of his paper he had chanced to meet with the observations of Hodgkin in the seventeenth volume of the *Medico-Chirurgical Transactions*, and lamented that "Doctor Hodgkin did not affix a distinctive name to the disease." But, even so, it was not until 1865 that Wilks⁵ really clarified the clinical entity by describing 15 cases, "13 of which resembled in all particulars the first 4 [*sic*] which Mr. Hodgkin first brought under the notice of the profession." At that time, Wilks apparently recognized even more clearly than did Hodgkin that among conditions affecting "the lymphatic glands and the spleen" there was a distinct and separate pathologic entity, for he wrote: "This disease of Hodgkin is clearly separable from lardaceous disease, from cancer, and tubercle, although these affections may bear a relation to one another. It is, however, as much a disease sui generis as any other and deserves a description of its own." Wilks noted the generalized lymphadenopathy, the splenomegaly and the not infrequent involvement of the liver, kidneys and lungs. He drew particular attention to the "remarkable anemia," and it is clear that he separated the condition sharply from the leukemias.

Knowledge of the condition was, however, still in a nebulous state, and it was not until 1878 that Greenfield¹⁴ described, insofar as he was able with the equipment of his day, not only the gross but also the microscopic appearance of the involved tissues. Greenfield evidently used the terms "Hodgkin's disease" and "lymphadenoma" interchangeably, for concerning his second case, one of "lymphadenoma," he wrote, "On section, the spleen presented very typically . . . the condition usually found in Hodgkin's disease." "In all five cases," he added, "the change in the gland was of the same kind. It consisted essentially in a sort of chronic inflammation involving especially the fibrous stroma of the glands which became thickened and gradually obliterated entirely the interstices so that the gland became a mass of dense, tough, fibrous tissue with little or no adenoid structure. . . . In the early stages, there was some general enlargement of the

glands, the fibrous stroma appeared coarser and there were a large number of multinucleated cells adherent to the trabeculae." In a similar manner, he reported: ["The normal structure of the spleen] in the affected parts appears to be entirely lost; it is everywhere traversed by irregular broad bands of fibrous tissue, which in many parts looks as much like sections of tendons as anything. At their edges, and in small places left between them are seen cells of various sizes massed together, a good many large multi-nucleated cells being amongst them."

Greenfield, too, distinguished Hodgkin's disease from leukemia. "In all five cases of typical lymphadenoma here shown," he wrote, "the blood was examined and no increase whatever of leucocytes observed, so that as far as my own experience in ten cases is concerned, I have no ground for believing in the presence of leucocythemia in typical cases of Hodgkin's disease."

Thus, Greenfield in 1878 first brought to the attention of pathologists the increase of fibrous tissue and the presence of multinucleated giant cells. He further noted that "clinically the disease, when well marked, exhibits an irregular febrile course, periods of latency and progress, a marked and peculiar anemia."

A further chapter in the histopathology of the disease was written by Goldmann,¹⁵ who in 1892 noted the frequent presence of eosinophils in the diseased tissue. In 1898, Sternberg¹⁶ discussed at great length what he believed at that time to be a peculiar form of tuberculosis masquerading as "pseudoleukemia," and described in detail the characteristic giant cells and the areas of necrosis. Thus, by 1898 both the main clinical features and the chief histologic findings had been elucidated and Hodgkin's disease had emerged as a definite and clearly recognizable entity.

It remained for Reed¹⁷ in 1902 and Simmons¹⁸ in 1903 to place the knowledge of the condition on a still firmer footing by their accurate and careful studies of the pathological findings in conjunction with the clinical histories. Reed concluded her study in 1902 by saying:

We believe, then, from the descriptions in the literature and the findings in eight cases examined, that Hodgkin's disease has a peculiar and typical histological picture, consisting of proliferations of the endothelial and reticular cells, formation of lymphoid cells and characteristic giant cells and a gradual increase of connective tissue, resulting in fibrosis and, in most of the specimens, in the presence of great numbers of eosinophils.

It must, perhaps, remain a matter of personal choice whose name should be assigned to the ever-present and diagnostic giant cells. Without doubt, they were recognized by Greenfield in 1878, and their characteristics were fully depicted by Sternberg in 1898, but Sternberg had the misfortune to study a series of cases of Hodgkin's disease combined with active tuberculosis, and only in his later years did he give up the idea that he was dealing

with a peculiar form of tuberculosis. Perhaps the greatest credit should go to Reed, who described the cells even more accurately than did Sternberg and who recognized clearly that they were an integral part of the disease described by Hodgkin seventy years before.

Hodgkin's sarcoma. The concept that Hodgkin's granuloma may become transformed into Hodgkin's sarcoma is sometimes traced to Yamasaki,¹⁹ but the histologic descriptions of the "tumor" from his 2 cases in no way substantiate his claim, which is indeed supported solely by the title of his paper. Welch²⁰ reported a case from which a biopsy six months before death showed Hodgkin's granuloma. Autopsy showed widespread involvement by what may well have been a sarcoma developing from a granuloma. Ewing⁴ wrote in 1928, "The transformation of Hodgkin's granuloma into a sarcomatous process occurs in a certain proportion of cases," and added: "The structure varies from a close counterpart of Hodgkin's granuloma to a tissue composed exclusively of large round cells with faintly staining cytoplasm and moderately chromatic vesicular nuclei. Large round giant cells with multiple or multilobed nuclei predominate."

Comparatively few authors refer to this, the most fulminating, form of Hodgkin's disease, although, as Ewing rightly points out, "Many cases described in the literature as lymphosarcoma are probably of this nature."

NATURE OF THE DISEASE

Hodgkin's Paragranuloma

Hodgkin's paragranuloma bears little or no resemblance to a true tumor, either in its histologic picture or its clinical course. The often scattered, isolated Reed-Sternberg cells, the lymphocytic infiltration with or without destruction of the lymph follicles and the complete lack of invasiveness all bespeak an infectious process, as do the comparatively benign course and the fact that in almost all cases the disease starts in the lymph nodes of the neck, to which the causative agent may have gained access through the pharynx. It is not improbable that the paragranulomatous form bears to the granulomatous type of the disease the same relation that a primary tubercle does to fibrocaceous tuberculosis.

Hodgkin's Granuloma

As might be expected from the varied terminology already referred to, opinions concerning the nature of the granulomatous type of the disease are equally at variance. Billroth⁷ and Benda⁸ were firmly convinced that it was a malignant neoplasm. In this country, this concept has been upheld by Warthin,²¹ Mallory¹⁰ and others. The contrary view — namely, that the condition is an inflammatory or infectious disease and not a neoplasm — has been advocated by Sternberg,² Fraenkel,²² Terplan and Mittelbach²³

and many other workers, both abroad and in this country.

Still another group of authors believe that the granulomatous type represents a combination of an inflammatory and a neoplastic process. Thus, Chevalier and Bernard²⁴ have suggested that it may be an inflammatory reaction due to a virus and that it later changes into a blastoma as do the infectious epitheliomas.

As has been said above, the fact that the Reed-Sternberg cells are frequently scattered, isolated and often separated widely by cells of other types favors an inflammatory process rather than a neoplasm, for certainly in no true tumor does this condition obtain. On the clinical side, the irregular bouts of fever, seldom absent in the more advanced stages and often seen to a less degree early in the course, and more especially the relapsing type commonly called "Pel-Ebstein fever," the marked anemia in absence of bleeding or widespread invasion of the marrow, the polymorphonuclear leukocytosis and the prominent and persistent tachycardia are all more characteristic of an infectious process than of a tumor.

Hodgkin's Sarcoma

Hodgkin's sarcoma has, in our opinion, all the characteristics of a true neoplasm. The uniformity of the cellular constituents, the aggressive, invasive nature of the process, the extremely short duration of life and the not uncommon finding of a large destructive tumor with comparatively few metastases all favor this concept. So also does the fact that the disease is commonest in the sixth and seventh decades and is extremely rare below the age of thirty. This view, however, is contrary to that held by many workers, such as Sternberg² and Kaufmann,²⁵ who maintain that this cellular type is merely a variant of the granulomatous form and is of the same basic nature. As already noted, however, Ewing⁴ speaks of sarcomatous transformation in certain cases of Hodgkin's disease, and we have made similar observations in our own cases.

ETIOLOGY

If our concept of the disease is correct, the etiology of the paraganulomatous form is identical to that of the granulomatous. The granulomatous form is not brought into existence, for the time, owing either to relative immunity on the part of the host or to comparative lack of virulence on the part of the exciting agent.

Historical Summary

Many authors have emphasized the importance of the tubercle bacillus as the etiologic agent in Hodgkin's granuloma. Sternberg¹⁶ originally described the lesion as an atypical form of tuberculosis (8 out of 13 of Sternberg's original series of

cases were complicated by definite tuberculosis). Lichtenstein²⁶ claimed to have produced Hodgkin's granuloma in guinea pigs by the injection of material from human cases and of tubercle bacilli. Fraenkel and Much²⁷ demonstrated antiformin-resistant, gram-positive granules in granulomatous tissue that showed no demonstrable evidence of tuberculosis. Furthermore, by injections of large amounts of antiformin-treated material, they succeeded in producing not only tuberculosis but also lesions that in their opinion resembled those of Hodgkin's granuloma.

L'Esperance^{28, 29} claimed to have shown that the etiologic agent was an avian strain of tubercle bacilli. Her work could not be confirmed by other workers, including van Rooyen,³⁰ Branch³¹ and ourselves.

Perhaps an equal number of investigators have denied the etiologic role of tuberculosis in the production of Hodgkin's granuloma. Both Reed¹⁷ and Longcope,³² whose publications amplified Sternberg's original description of the disease, denied the identity of Hodgkin's granuloma with tuberculosis. Terplan and Mittelbach,³³ as a result of their own experiments and a review of the literature, held the same view. They believed that in those cases in which positive evidence for tuberculosis was obtained, the tubercle bacillus was either a secondary or coincident invader and was in no way causative of the Hodgkin's disease. Furthermore, these authors were not convinced that Hodgkin's granuloma had ever been produced in experimental animals. Uddstromer³³ in his study of 548 cases of Hodgkin's granuloma likewise found no support for the thesis that tuberculosis is the causative agent.

The literature on this particular aspect of the problem is exceedingly extensive, and the reader who wishes further details is referred to the reviews by Wallhauser,¹ Sternberg,² Terplan and Mittelbach³³ and Simonds.³⁴

The tuberculin test has been employed by various investigators in an attempt to prove or disprove a direct relation between the two diseases. Cases of Hodgkin's granuloma have almost uniformly been anergic, reacting, if at all, only to low dilutions — 1:10 or 1:100, rarely 1:1000. The test often becomes positive, frequently strongly so, after effective x-ray therapy.

It should be emphasized that Hodgkin's granuloma is frequently complicated by tuberculosis. According to Ziegler³⁵ and other workers, this occurs in 15 to 25 per cent of cases. In our own series, we found coexistent active tuberculosis in 20 per cent. The fact that one may find in the same patient or even in the same organ both Hodgkin's granuloma and tuberculosis has seemed to us to indicate the lack of identity of the two diseases, for it appears highly improbable, if not impossible, that a host should react in two entirely distinct ways to the

same-micro-organism. Furthermore, if the tubercle bacillus is actually the cause of Hodgkin's granuloma, the disease should be found more commonly in persons suffering from proved tuberculosis than in those free of the disease. Such does not appear to be the case. Medlar³⁶ found Hodgkin's disease in only 0.3 per cent of patients who had tuberculosis and were followed until death at the Metropolitan Life Insurance Company Sanatorium, and of 2297 cases of tuberculosis coming to autopsy at the Boston City Hospital, only 7, or 0.3 per cent, showed Hodgkin's disease as well. This figure is not significantly higher than the general incidence of Hodgkin's granuloma (see below). Furthermore, Uddstromer³⁵ in his careful analysis of the situation in Sweden found that Hodgkin's disease was less common in areas in which the tuberculosis rate was high than in those in which it was low.

Various diphtheroid bacilli have also been claimed as the etiologic agent by a number of investigators. Among these may be mentioned Bunting and Yates,³⁷ DeNegri and Mieremet,³⁸ Bloomfield³⁹ and Torrey.⁴⁰ Bunting and Yates named their organism *Bacterium hodgkini* and claimed that injections into animals produced Hodgkin's granuloma. Others have not been able to confirm their work, however, and numerous investigators have found diphtheroid bacilli in lymph nodes from a variety of other conditions, such as lymphosarcoma, metastatic carcinoma and tuberculosis. It is now generally held that such diphtheroids as have been identified are not of etiologic importance.

It has also been claimed⁴¹ that amebas are the cause of the disease. There has been no confirmation of this claim.

Recently Gordon^{42, 43} in England found that material from Hodgkin's granuloma injected intracerebrally into rabbits produced paralysis that usually resulted in death. Negative results were obtained with the material from cases of carcinoma, sarcoma and with other pathologic tissues. Gordon concluded that this was a satisfactory diagnostic test, and he believed, furthermore, that the disease was due to a specific pathogenic agent, probably a virus, although he was unable to transmit it from rabbit to rabbit. Van Rooyen⁴⁴⁻⁴⁶ confirmed Gordon's results in so far as the test was concerned. In collaboration with Turner, we⁴⁷ demonstrated that the Gordon test is apparently entirely dependent on the presence of eosinophils and is in no way specific for Hodgkin's disease. Our work has been confirmed by Edward,⁴⁸ McNaught⁴⁹ and King.⁵⁰

Another group of workers believes that Hodgkin's granuloma is a special — by some considered allergic — type of reaction of the tissues to any of the usual pyogenic organisms and that the disease, therefore, has no single etiologic agent.

The latest contributions of note on the subject of etiology are those of Parsons and Poston⁵¹ and Wise and Poston.⁵² In the latter paper it is reported

that cultures of lymph nodes from 14 consecutive cases of proved Hodgkin's granuloma yielded positive cultures for organisms of the Brucella group. They further found that such patients were anergic to abortin. Cultures from 67 cases with diseases of lymph nodes other than Hodgkin's disease with one exception yielded negative results. It is as yet too early to pass final judgment on the significance of these findings. To date, we have been unable to confirm them.

Twort⁵³ in an extensive study of the etiology of Hodgkin's granuloma, using a great variety of cultural methods, obtained entirely negative results.

Bacteriologic Studies

For three years, we cultured lymph nodes removed aseptically at surgical operations on an egg medium suitable for growing tubercle bacilli. Approximately seventy-five nodes from patients with a variety of diseases were so cultured. In no case did material from a Hodgkin's granuloma yield a positive culture for *Mycobacterium tuberculosis*, whereas material from tuberculous nodes gave uniformly satisfactory growths of the organism. It should be noted that in 3 cases of Hodgkin's granuloma, smears made from the apparently negative surfaces of the inoculated slants of egg medium showed acid-fast bacilli. These would not grow in subculture, and their nature is entirely obscure.

In addition to the egg medium used, we also cultured the last fourteen nodes of this first series in dextrose ascitic-fluid broth sealed with vaseline, as well as in ascitic-fluid broth and brain broth and on blood agar. Four of the nodes so cultured, three from cases of Hodgkin's granuloma and one from a case of Hodgkin's paraganuloma, yielded a growth of a small gram-positive, strictly anaerobic, gas-forming bacillus. In smears of cultures, the organisms occurred in clumps and chains. Because of this finding and the negative results of our efforts to demonstrate the tubercle bacillus, we discontinued our cultures for the latter and concentrated on culturing for this anaerobic bacillus. For this purpose, we used chopped-meat broth sealed with vaseline, a medium that we had found favorable for its growth.

Eighty-one lymph nodes were cultured in this medium. The organism was obtained from a considerable number of cases of Hodgkin's disease but by no means all. It was, however, cultured also from cases with other forms of lymphoma and from nodes involved by carcinoma, tuberculosis and chronic inflammation. A positive blood culture for this organism was obtained from a febrile case of Hodgkin's granuloma (J. A., S36-1092) at the height of the fever, whereas cultures were negative when the temperature was normal. A positive blood culture of a similar organism was, however, likewise obtained from a patient who so far as was known did not have the disease.

Attempts to demonstrate a relation of this organism to Hodgkin's disease by means of agglutination and skin tests failed. The bacillus was not pathogenic for the usual laboratory animals—rabbits, guinea pigs and mice. Its significance, therefore, remains doubtful.

A series of nodes were also cultured in sheep's blood broth and on blood-agar plates and slants, the latter being incubated under normal atmospheric conditions and under increased carbon dioxide tension (10 per cent). The results were consistently negative save for the rare presence of a readily recognized contaminant, such as a staphylococcus. It should be mentioned here in connection with our technical procedure that such contaminations were uncommon.

Animal Inoculations

Portions of the lymph nodes used for culturing for tubercle bacilli were also injected into rabbits, guinea pigs and pigeons. The rabbits were inoculated intravenously, subcutaneously and, rarely, intracerebrally, the guinea pigs intraperitoneally and subcutaneously, and the pigeons intravenously and intraperitoneally. All the animals were kept for from several months up to one and a half years before being killed and autopsied. In the entire group of animals inoculated with material from Hodgkin's granuloma, only one guinea pig showed tuberculosis, the organism proving to be a bovine strain. This node was from a child aged ten years (M. G., S28-1804) and microscopically showed no evidence of tuberculosis, but rather what appeared to be an uncomplicated picture of Hodgkin's granuloma. Nodes from the other forms of Hodgkin's disease and other types of lymphoma as well as carcinomatous nodes and inflammatory nodes gave negative results. As was to be expected, all material from cases of tuberculosis produced that disease in the animals.

Tuberculin Reactions

As reported in a previous paper,⁵⁴ we carried out a series of intracutaneous tuberculin reactions using both human and avian tuberculin. The patients so tested comprised sufferers from a variety of diseases besides Hodgkin's granuloma and included a number known to have active tuberculosis. The patients with Hodgkin's granuloma showed a definite anergy to both types of tuberculin. The significance of this anergy is entirely obscure, but it suggests that tuberculosis is not the cause of Hodgkin's granuloma; furthermore, if an untreated case of proved Hodgkin's granuloma reacts positively to high dilutions of tuberculin, this indicates that the patient also has active tuberculosis.

In considering all the evidence at hand from reports in the literature and from our own work, we

are forced to conclude that the etiology of Hodgkin's granuloma has yet to be discovered.

INCIDENCE

Hodgkin's granuloma is, fortunately, an uncommon disease. Uddstromer⁵³ found only 548 cases in the whole of Sweden between 1915 and 1931, an incidence of 0.054 cases per 10,000 living persons as based on the average population of the country during that period. All cases were proved by biopsy or autopsy, and all tissue was examined by the author himself. Among 8485 general autopsies, Symmers⁵⁵ found 14 cases of Hodgkin's disease, and in Barron's⁵⁶ 7253 autopsies there were 24 cases. The combined incidence as estimated from these two latter series is 0.23 per cent. Ciechanowski⁵⁷ found an incidence of 0.33 per cent in 60,000 autopsies.

In our own series of 259 proved cases,* the total available figures must be broken down, for many cases were admitted to the Collis P. Huntington Memorial Hospital or the Pondville Hospital, two institutions that are devoted primarily to the care of patients with one or another form of malignant disease and likely, therefore, to have, in relation to the general population, a disproportionately large number of cases of Hodgkin's disease in their wards. A juster estimate of the incidence of the disease, so far as our own experience is concerned, may be derived from the figures at the Boston City Hospital.

TABLE 1. *Age at Onset of Hodgkin's Paragranuloma.*

AGE yr.	NO. OF CASES	PER CENT
0-9	2	5
10-19	6	16
20-29	9	24
30-39	6	16
40-49	4	10
50-59	4	10
60-69	6	16
70-79	1	3
Total	38	

At this institution, there were 16,773 autopsies from 1897 to 1943, and among these 35 showed Hodgkin's granuloma, an incidence closely approximating that of the combined figures of Symmers⁵⁵ and Barron⁵⁶ referred to above. It should be emphasized that all our autopsy and biopsy material of whatever date has been comprehensively reviewed by us personally during the last three years, so that in all cases the diagnosis has been made in the light of the most recent histologic knowledge.

We may tentatively conclude that Hodgkin's granuloma accounts for approximately 0.25 per cent of deaths in a general hospital.

Uddstromer⁵³ found the condition six times as common in 1931 as in 1915. He was hesitant in say-

*From the total number seen, only those cases were included from which we had at the time of study satisfactorily stained tissue and on which we had adequate clinical data, at least for the patient's first visit to the hospital.

ing that there had been an actual increased rate. Our data do not support the view that the disease is on the increase.

AGE AND SEX

Hodgkin's Paragranuloma

The age incidence of Hodgkin's paragranuloma is shown in Table 1; it roughly parallels that of the granulomatous form (see below). Of 38 patients, 27, or 71 per cent, were males.

Hodgkin's Granuloma

Although it has been repeatedly stated that Hodgkin's granuloma principally affects young adults, it is of the greatest importance to recognize that the condition may occur at any age. In the literature, there is no consensus concerning the decade in which it is most commonly seen, and some confusion has arisen from the facts that certain authors derive the age incidence from the date of the first symptoms, that others have recorded their cases according to the age at death, and that still others have contented themselves by saying that the disease "occurred in" certain decades.

Uddstromer,³³ who carefully dated his cases from the first symptom that could properly be attributed

TABLE 2. *Age at Onset of Hodgkin's Granuloma (Uddstromer's³³—536 cases).*

AGE yr.	PER CENT
0-9	6
10-19	9
20-29	24
30-39	19
40-49	14
50-59	14
60-69	11
70-79	3

to the disease, found that the condition was commonest in the third decade, but his figures (Table 2) indicate clearly that no age group is spared.

On the other hand, in Longcope's³² series of 109 cases, 19 per cent occurred in the first decade of life, and of Smith's³⁸ 138 cases, over 12 per cent were seen under the age of ten. In sharp contrast, Sternberg² reports 29 per cent of his autopsied cases as falling in the sixth decade and 25 per cent in the seventh, and Priesel and Winkelbauer³⁹ report a case of a child who apparently had the disease at birth and died at the age of four months. It is thus apparent from a study of the literature that no age is spared and that the condition is found with reasonable constancy throughout the first seven decades of life. Our own experience confirms this view, for our cases are distributed quite evenly from earliest childhood to the age of 70 (Table 3).

Wallhauser¹ believed that the number of cases developing during the period of puberty was sur-

prisingly and significantly small, since he found that of 33 cases in patients under fifteen, only 2 occurred between the ages of twelve and fourteen. Similarly, in Uddstromer's series of 57 cases with onset under the age of sixteen, only 6 came down with the disease "in the period of puberty," and of our own 43 patients under the age of sixteen, only

TABLE 3. *Age at Onset of Hodgkin's Granuloma.*

AGE yr.	NO OF CASES	PER CENT
0-9	27	11
10-19	32	14
20-29	41	17
30-39	35	14
40-49	37	16
50-59	32	14
60-69	25	11
70-79	7	2
80-89	1	1
Total	237	

6, all boys, were first stricken between the ages of twelve and fourteen. As Uddstromer points out, however, the number of cases in the childhood period is so small that one must be cautious before drawing any broad conclusions on this particular point and, furthermore, the age at which puberty begins varies over rather wide limits in different latitudes and in various races.

For the present, the most important consideration is the undeniable fact that Hodgkin's granuloma may occur at any age, although it appears to be uncommon in infancy and in extreme old age.

There is general agreement that Hodgkin's granuloma is commoner in males than in females. Nearly 70 per cent of the patients in the 1447 cases collected from the literature by Wallhauser and 61 per cent of Uddstromer's 548 patients were males. This preponderance becomes even more marked in children, for 91 per cent of Uddstromer's and 94 per cent of Smith's patients under the age of ten were males. In our own series of 237 patients, 70 per cent were

TABLE 4. *Age at Onset of Hodgkin's Sarcoma.*

AGE yr.	NO OF CASES	PER CENT
0-9	0	0
10-19	0	0
20-29	2	4
30-39	8	16
40-49	6	12
50-59	14	27
60-69	14	27
70-79	7	14
Total	51	

males, and almost precisely this proportion was maintained in the childhood group. There does not appear to be any adequate explanation for this sex difference.

It is our belief that Hodgkin's granuloma occurs more frequently in members of the same family than can be accounted for by chance alone.

Hodgkin's Sarcoma

Hodgkin's sarcoma occurs chiefly in the middle-aged or elderly (Table 4). Eighty per cent of our 51 patients were over forty years of age. In no case have we seen a patient with primary Hodgkin's sarcoma—that is, not preceded by Hodgkin's granuloma—under twenty years of age. Twenty-six, or 51 per cent, of our patients were men. It is apparent, therefore, that both the age and the sex distribution differ sharply from those of Hodgkin's granuloma and paraganuloma.

SUMMARY

Hodgkin's disease, in our opinion, should be subdivided into the paraganulomatous, the granulomatous and the sarcomatous type. The nature, etiology and incidence of these three varieties have been discussed; their pathologic and clinical pictures and their treatment will be considered in subsequent articles.

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THE DENTAL NEEDS OF MASSACHUSETTS CHILDREN OF TODAY*

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THE deplorable condition of the teeth of the young men of this country has been made prominent by the fact that dental defects have been the greatest single cause for rejection by the armed services. Massachusetts, in common with other New England states, has in this particular a record far worse than those of other sections of this country. That this regional record of relatively poor dental conditions is not a recent development is indicated by the fact that approximately the same rate of rejections for dental defects obtained in the Civil and Spanish-American wars and in World War I. In World War I, the rate for Massachusetts was 78.82 per 1000 men, whereas in Arkansas it was only 2.90 per 1000 men examined.¹ It might be thought that this great variation could be explained on the basis of different standards of dental examinations. This is probably not so, since the examinations were made at the camps by Army officers; furthermore, similar conditions were reported in the drafts of 1863 and 1864,² examinations made by Navy dentists agree closely with the figures reported from Army examinations³; and independent examinations of school children of ten to twelve years of age in Massachusetts and Maryland showed approximately twice as great an incidence of dental caries in the Massachusetts children.^{4,5}

The chief cause of loss of teeth in young adults is tooth decay. It might be assumed that this condition occurred to a similar degree in New England and in the rest of the United States, but that dental caries was less well treated and controlled here than elsewhere. A great deal of evidence indicates that such an assumption is not justifiable. For example, in a recent survey made by the Committee on Economics of the American Dental Association,⁶ it is stated that there is evidence of more adequate professional care in this section of the country than in any other. In addition, the proportion of dentists to the total population and the per capita amount spent for dental services are relatively high here. The conclusion is unavoidable that the incidence of tooth decay is actually higher here than elsewhere.

Tooth decay, once started, usually continues to destroy more and more of the tooth substance. Left untreated it almost inevitably leads to pulp abscess

and loss of the affected tooth. Detection of incipient caries by frequent inspections and x-ray examinations, removal of the diseased tooth structure and restoration of the normal tooth contours by means of fillings constitute accepted dental practice. Competent and continuous professional care can decrease the loss of permanent teeth in adolescents to practically zero. If such a program were started with every three-year-old child in the Commonwealth and carried through until the age of eighteen, there is little doubt that the major cause of loss of teeth, and hence of rejections for physical defects of a dental nature, would be eliminated. This program would be expensive and would require the training of additional personnel, but the returns in physical well-being and appearance and in freedom from pain would be of great value. Sweden⁷ and New Zealand⁸ have had experience with extensive programs designed to ensure a sound dentition for every child. The British⁹ and Canadian¹⁰ programs for compulsory health insurance, and the United States Social Security¹¹ program have been concerned with dental problems. The principle that the health of the individual is the concern not only of the individual himself, but of society as a whole seems destined to become the keynote of future public-health programs. The part that the dental profession may play in such a program is already a subject of study by the Massachusetts State Dental Society. Your committee recommends that the Massachusetts Central Health Council approve in principle the goal of adequate dental care for all children up to the age of eighteen.

The problem of providing dental care for boys approaching the draft age is an immediate one. There is no doubt that loss of teeth can be prevented by adequate dentistry. The provision of professional dental care is difficult at the present time when so many of the younger dentists are in service. The various dental organizations might well explore the possibility of more active co-operation with the Procurement and Assignment Service in its efforts to supply adequate professional service to all communities in the Commonwealth. Since even in peacetime it is estimated that approximately 70 per cent of the population receive no dental care other than treatment for the relief of pain, the magnitude of the problem under present conditions becomes apparent. The long period of training for the practice of dentistry makes it imperative that the time and skill of the dental operator be efficiently utilized. Relatively few dental practitioners

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have studied the problem of attaining maximum productivity by the use of assistance, planned steps in operative procedure and the designing of equipment for efficiency rather than for show. The dental schools might well undertake to train students in time-saving methods of operating, since cumbersome procedures learned in school may persist as the habits of a lifetime. Dental schools might also assume responsibility for the training of dental assistants and laboratory technicians. The dental hygienist has already demonstrated her usefulness in dental practice and to some extent in school and hospital clinics. A much wider use of her services for dental examinations and possibly for simple operations, in addition to the cleaning of teeth, which is now permitted, might be considered. This would necessitate a longer period of training than at present, which would doubtless be advantageous in other respects.

Most of the dentistry for the people of Massachusetts is done by private practitioners. A significant part of the dental care for children is provided in the clinics of the Forsyth Dental Infirmary, the Harvard and Tufts dental schools and various smaller clinics, especially those maintained in primary and grammar schools. The latter are particularly handicapped at the present time because of the shortage of dentists. In general, recent graduates have served such clinics on a part-time basis while building up their private practices. It is chiefly these men who have gone into service, and no one is available to take their places. The immediate problem can be met only by using most efficiently the time of those who are left, a subject that has already been discussed.

Thought should be given, however, to the post-war program. It appears evident that adequate dental care can be made available to all the children of Massachusetts only by the use of public funds. This would provide dental care for all in the same way that a public-school education is provided without regard to the ability of the child's family to pay for such services. It would not eliminate private practice, just as private schools are not eliminated by the public schools. It would ensure adequate dental care for the total child population rather than for the minor part, as at present. This would necessitate creating opportunities in public-health dentistry that would appeal to young men and women as a career. Such positions should be under civil service and should offer security of position and opportunity for advancement as well as for service, in compensation for the greater financial rewards of private practice.

An important feature of such a program would be its continuity. Sporadic dental care may be completely ineffective in preventing loss of teeth. It is the opinion of the members of your committee that dental services should be available throughout the high-school period. To care for the teeth of children

through the primary-school and grammar-school years and then neglect them through four years when caries susceptibility is high is likely to make the work of previous years of little avail. It seems probable that such a program would benefit rather than harm private practitioners of dentistry, since it would inculcate habits of regular dental care up to the time when most persons become self-supporting.

At present the Massachusetts Department of Public Health has a dental unit consisting of two dentists and two dental hygienists. Despite the fact that Massachusetts was one of the first states to include dentistry in its public-health program, the appropriation for this purpose at the present time is less than 0.5 per cent of the total public-health budget, and this contrasts unfavorably with many other states. For example, in 1938, the proportion of the state budget allotted to dental-health programs was 3.1 per cent in Connecticut and 5.6 per cent in North Carolina.¹²

The members of your committee believe that the dental unit should eventually become a full division in the Department of Public Health. They recommend that the Commissioner of Public Health appoint an advisory council to this dental unit. This council might consist of representatives of the Massachusetts State Dental Society, the Oral Hygiene Council, the Forsyth Dental Infirmary, the Harvard School of Dental Medicine and the Tufts College Dental School. The advisory council could be of great assistance to the dental unit in planning a program to meet the dental needs of the people of Massachusetts.

So far we have been concerned with the problem of tooth decay and the steps that may be taken to arrest its progress and repair the damage it causes. What about the prevention of dental caries? Prevention is usually dependent on a knowledge of etiology, and the etiology of dental caries is unknown. Certain observations, however, appear to be well established: dental caries always starts on the outer surfaces of teeth; tooth structure is destroyed by the action of acids; a number of bacterial species found in the mouth are capable of producing acids; and sugars and starches constitute a favorable pabulum for these acidogenic bacteria. Whether these are primary or secondary causes cannot yet be decided. Such observations afford the rationale for attempts at preventing tooth decay by cleansing the teeth, and for the use of alkaline toothpastes and mouthwashes. The prevalence of tooth decay in spite of the expenditure of large sums on toothbrushes and dentifrices indicates that such measures are not effective.

Considerable evidence is available that sugars and starches promote the initiation and progress of tooth decay, and that the incidence of dental caries may be reduced by lessening the amount of these substances in the diet. It is quite possible that

wartime rationing of sugar and candies may lessen the amount of tooth decay in children.

A most important advance in the understanding of the effect of nutrition on the development and maintenance of a healthy dentition. Good nutrition, especially during the developmental periods of the teeth, is generally recognized as a fundamental factor in dental health, although the mechanism by which this factor exerts its influence is a matter of dispute. Many investigators have reported a correlation between nutritional improvement and reduction of dental caries in children.

It is obvious that efforts to promote dental health through adequate nutrition should be correlated with, and indeed should be a part of, the more general nutritional program. Utilization of the present knowledge and equitable distribution of the available food supply would ensure better health, including better teeth. The fact should not be overlooked that teeth are digestive organs, and that normal mastication and salivary digestion cannot occur when the teeth are diseased or lacking. A well-selected diet may not be adequate if it is not properly digested, and the teeth play a part in the digestive process. Furthermore, it should be pointed out that eating habits are of importance in maintaining sound teeth. It is well established that such a simple procedure as finishing a meal with an orange or an apple rather than with cake or candy may be associated with relative freedom from tooth decay. This effect seems explainable chiefly on the local cleansing action of the fruit as opposed to the debris left on the teeth by the pastry, rather than to the superior nutritional value of the fruit.

The striking laboratory and clinical data now appearing in the literature concerning the effectiveness of small amounts of fluorine (less than 2 parts per million) in preventing tooth decay in human beings as well as in laboratory animals¹² have been considered by this committee. Although we are not ready to recommend the widespread use of this substance as a public-health measure, we believe that continued study of this phase of the problem should be made, and suggest that it might be used under proper supervision in some section of the

Commonwealth so that data may be obtained concerning its effectiveness in a region of the country where dental caries is most nearly universal.

A final word should be said concerning the responsibility of the medical profession for the control of dental disease. It is unfortunate that most physicians neglect to examine the mouths of their patients with the same care and attention paid to other parts of the body. The treatment of dental disease is the province of the dentist, but its recognition is equally the responsibility of the physician.

SUMMARY

Dental caries is a more serious problem in Massachusetts than in other sections of the country.

Early detection and treatment is an effective procedure, but it requires highly trained personnel and is therefore expensive. Ways of more efficient use of this personnel are suggested.

The promotion of a public-health dental service is discussed. The appointment of an advisory council to the dental unit of the Massachusetts Department of Public Health is recommended.

The etiology of dental caries is discussed, and the role of nutrition in controlling its ravages is commented on.

The responsibility of the medical profession for the recognition of dental disease is stressed.

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PHENARSINE HYDROCHLORIDE IN THE TREATMENT OF SYPHILIS

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PHENARSINE hydrochloride is a mechanical mixture of 3-amino-4-hydroxy-phenyl-dichlorarsine hydrochloride with sodium citrate as a buffer diluent. Its chemical constitution and pharmacologic properties have been fully described by Long¹ and Guy, Goldmann and Gannon.²

The treatment of syphilis with phenarsine was begun in the Department for Diseases of the Skin of the Boston City Hospital one and a half years ago. The drug† was given in courses of ten to twenty injections, alternating with courses of fifteen injections of bismuth. The doses ranged from 0.030 to 0.045 gm. for women and from 0.030 to 0.067 gm. for men. In cases of primary and early secondary syphilis three injections a week were given for the first two or three weeks, and weekly injections after that to the end of the first course of arsenicals.

actions. One of these also had an eruption, and 1 developed jaundice and hypochromic anemia (Table 2). The treatment was changed to Mapharsen in 2 cases, to neoarsphenamine in 2, and to bismuth in 1, and 2 patients failed to report for further treatment. The patient who had jaundice and hypochromic anemia was a thirty-four-year-old Negress with primary seropositive syphilis and a positive dark-field examination. She developed jaundice and tenderness over the liver after having received seven injections (300 mg.) of phenarsine within two and a half weeks. The blood at that time showed a hemoglobin of 63 per cent, 3,360,000 red cells and 5800 white cells, with 71 per cent polymorphonuclear neutrophils, 2 per cent eosinophils, 1 per cent basophils, 20 per cent small lymphocytes and 6 per cent monocytes; the platelet count was normal.

TABLE 1. Summary of Data.

	TYPE OF SYPHILIS			
	PRIMARY	SECONDARY	LATE	ALL TYPES
Number of patients	14	31	67	112
Dropped	7	24	34	65
Remained under treatment	7	7	33	47
Cases with reactions	5 (36%)	8 (26%)	12 (18%)	25 (22%)
Drug discontinued because of reactions	2 (14%)	2 (6%)	3 (4%)	7 (6%)
Reactions:				
Nausea, vomiting and diarrhea	3	5	11	19
Jaundice and anemia	1			1
Eruptions	1	3	1	5
Total injections of phenarsine	131	391	777	1299
Total dosage of phenarsine	10416 mg.	18013 mg.	32928 mg.	61357 mg.

In later courses it was administered at weekly intervals throughout the courses. Bismuth subsalicylate in peanut oil was used in weekly doses of 1 cc. (0.075 gm. of bismuth) for fifteen doses. Phenarsine and bismuth were never given simultaneously. Cases of late syphilis received a course of bismuth at the beginning of treatment. Pregnant women were treated with phenarsine only. It was given to 112 patients who made regular visits (Table 1). This group included 14 cases of primary, 31 cases of secondary and 67 cases of late syphilis (early and late latent, and tertiary). During the period mentioned 65 patients dropped out for various reasons; 58 were transferred to other clinics, chiefly because they were near their places of employment, and the remaining 7 could not be traced.

Five patients had to discontinue the phenarsine treatment because of severe gastrointestinal re-

Treatment was continued with bismuth and the patient's condition improved rapidly. Four months later the hemoglobin was 78 per cent, the red-cell count 4,000,000, and the white-cell count 4250, with 69 per cent polymorphonuclear neutrophils, 2 per cent eosinophils, 9 per cent monocytes and 20 per cent lymphocytes. The red cells were slightly hyperchromic but normal in size and shape and the platelet count was normal. Five months after the beginning of treatment, the serologic reaction became negative and remained so. The patient has continued treatment with bismuth for fifteen and a half months and is in excellent health.

Mild reactions, mostly headache, dizziness and nausea, occurred in a number of cases. Five (36 per cent) of the 14 cases of primary syphilis showed some type of reaction. Among these, in only 2 cases were the reactions severe enough to cause discontinuance of phenarsine. Of the 31 patients with secondary syphilis, 8 (26 per cent) had reactions, but only 2 had to discontinue treatment. Of the 67 patients with late syphilis, 12 (18 per cent) showed reactions, but only 3 had to discontinue treatment.

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When reactions appeared, phenarsine was continued in smaller doses, with the addition of 10 cc. of 50 per cent glucose or 10 cc. of 10 per cent sodium thiosulfate, which benefited half the primary cases and about three fourths of the cases of secondary

lesions required 3.7 weeks. Disappearance of the rash in secondary syphilis required only 2.8 weeks. The average time required for all lesions in primary and secondary syphilis was therefore 3.14 weeks, or about twenty-two days.

TABLE 2. Cases Showing More than Mild Gastrointestinal Reactions.

CASE NO.	DIAGNOSIS	KIND OF REACTION	DOSE OF PHENARSINE mg.	SUBSEQUENT TREATMENT	REMARKS
1	Primary syphilis	Headache, nausea, vomiting and diarrhea	6200	Neosarsphenamine	
2	Primary syphilis	Hepatitis, jaundice and hypochromic anemia	7300	Bismuth	Seronegative after 5 mo.
3	Secondary syphilis	Vomiting and diarrhea	20922	Maparsen	Seronegative after 5 wk
4	Secondary syphilis	Headache, nausea and dermatitis	6380		Treatment discontinued
5	Secondary syphilis	Dermatitis	12760		Treatment discontinued
6	Late congenital syphilis	Vomiting and diarrhea	5225	Maparsen	
7	Late latent syphilis	Vomiting and diarrhea	7292	Neosarsphenamine	

and late syphilis. From these figures it can be seen that a higher percentage of reactions occurred in the early cases, which received three doses weekly for the first two weeks, than in the secondary or late cases. When the serologic reversals to negative are considered, however, the cases that had received this intensified treatment also showed later a higher incidence of reversals. No case of nitritoid crisis, renal damage, purpura, encephalitis, optic atrophy or permanent damage to the blood-forming organs occurred. The only case showing liver damage was

Serologic reversal (Table 3) occurred in 6 (86 per cent) of the 7 cases of primary syphilis, and in 6 (86 per cent) of the 7 cases of secondary syphilis. In the 33 cases of late syphilis, there were 3 reversals or 9 per cent. Therefore, in the 47 cases remaining under treatment there were reversals in 15 or 32 per cent.

In the cases of primary syphilis the average values of 14.3 injections of phenarsine (881 mg.) and 3.5 injections of bismuth over a period of 10.8 weeks were needed to accomplish reversal. For the group

TABLE 3. Cases Showing Serologic Reversal from Positive to Negative.

TYPE OF SYPHILIS	NO. OF INJECTIONS OF PHENARSINE	TOTAL DOSE OF PHENARSINE mg.	NO. OF INJECTIONS OF BISMUTH	TIME REQUIRED FOR REVERSAL	REACTIONS
Primary	6.0	270	16	4½ mo.	Nausea
	10.0	499	0	2 mo.	None
	10.0	636	5	2 mo.	None
	14	872	0	2½ mo.	None
	36	390	0	3½ mo.	Erythema of Milian
	10	360	0	1 mo.	None
Secondary	12.0	525	13	4½ mo.	Nausea
	12.0	540	15	5½ mo.	None
	18.0	810	10	5 mo.	Vomiting and diarrhea
	6.0	270	0	½ mo.	Vomiting and diarrhea
	4.0	180	5	4 mo.	Vomiting and diarrhea
	31.0	076	30	3 mo.	None
Late	10.0	420	30	10 mo.	None
	10.0	516	16	9 mo.	None
	10.0	633	15	6 mo.	None
Averages:					
Primary syphilis	14.3	881	3.5	10.8 wk.	
Secondary syphilis	13.8	567	12.2	15.2 wk.	
Late syphilis	10.0	523	20.3	33.3 wk.	
General average	12.7	657	12.0	19.8 wk.	

the primary case previously described. No serologic relapses were observed in the cases under treatment. In the cases of primary and secondary syphilis, the exact time required for healing of the lesions was recorded in only 7 cases. The healing of primary

with secondary syphilis the figures were 13.8 injections of phenarsine (567 mg.) and 12.2 injections of bismuth over a period of 15.2 weeks. The 3 cases of late syphilis received 10.0 injections of phenarsine (523 mg.) and 20.3 injections of bismuth over a

period of 33.3 weeks. The average figures in all the cases with reversals were therefore 12.7 injections of phenarsine (657 mg.) and 12.0 injections of bismuth over a period of 19.8 weeks. It is of interest that the only case of primary syphilis under treatment that did not become negative had received only twelve injections of phenarsine (495 mg.) and no bismuth over a period of eight weeks — in other words, less than the average treatment received by the other 6 patients. This patient still has a good chance to become seronegative, which would raise the total number of reversals in this group to 100 per cent. The same applies to the only remaining patient with secondary syphilis, who had received only seventeen injections of phenarsine (965 mg.) in twelve weeks of treatment. From Table 2 it can be seen that among the cases with serologic reversal there was a higher incidence of reactions than in others. Among 15 recorded cases, 6 had reactions such as nausea, vomiting and diarrhea. One patient with primary syphilis, a pregnant woman, developed erythema of Milian on the ninth day of treatment. Treatment was continued, and on her request she received three injections of 67 mg. of phenarsine weekly. Within three and a half months she had received thirty-six injections of phenarsine (2390 mg.). No bismuth was given. By the end of this period the serologic reaction had become negative and she delivered a healthy child. After this she was treated with weekly injections of bismuth and the serologic reaction remained negative.

Whereas the incidence of reactions in all cases of primary syphilis was 36 per cent, in those of secondary syphilis 26 per cent and in those of late syphilis 18 per cent, in cases with later serologic reversal the incidence was 40 per cent. Nevertheless, the

number of severe reactions was small, and only 1 case of jaundice with anemia occurred, with complete recovery.

With this low toxicity, phenarsine compares favorably with Mapharsen. So far as reversals are concerned, Gruhitz and Dixon³ state that cases of early syphilis treated continuously with Mapharsen and heavy metals show reversal to negative in 88 per cent after six months of treatment, and in 96 per cent after ten months of treatment. When it is considered that many of our patients have been treated a shorter time than this, our figures are certainly as favorable as those given for Mapharsen.

SUMMARY

In 112 cases of all stages of syphilis, phenarsine hydrochloride (Clorarsen) when given intensively caused a fairly high percentage of minor gastrointestinal symptoms, but in only 7 cases were these so severe that the treatment had to be stopped. There was only 1 case of liver damage and anemia, and this patient completely recovered. There was no mortality, and no other serious reactions occurred. There was no case of clinical or serologic relapse, and the percentage of serologic reversals from positive to negative was as high as that obtained with other arsenicals. We therefore believe that phenarsine is a safe drug, and our results appear to warrant further therapeutic investigation.

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MEDICAL PROGRESS

THE DIFFERENTIAL DIAGNOSIS OF CHICKEN POX AND SMALLPOX

CONRAD WESSELHOEFT, M.D.*

BOSTON

EIGHTY years ago an acrimonious controversy raged over Europe as to whether chicken pox (varicella) and smallpox (variola) were or were not the same disease.^{1,2} Both were endemic and epidemic at that time. The severe cases of chicken pox and mild cases of smallpox contributed to the confusion. Later there came into vogue the erroneous notion that chicken pox never attacks adults.³ Only within the past half-century have the two diseases been clearly differentiated. Indeed, they are entirely different. The classic picture of each can be recognized at a glance. Both, however, are subject to such wide variation that almost every point of differentiation may have an exception under certain circumstances. The importance of these points and their exceptions, particularly to military medicine, prompts this review.

EPIDEMIOLOGIC CONSIDERATIONS

Chicken pox is endemic in New England the year around. Epidemics usually begin in the colder months of the year and subside as summer comes on. In the Northern Hemisphere smallpox also occurs more frequently in the winter months.⁴ It was formerly both endemic and epidemic in New England, but of late has become pretty well extinct except for rare isolated outbreaks in communities where vaccination has not been properly enforced. It should be kept in mind that smallpox continues in the St. Lawrence Valley and that people from that area sometimes bring the disease to New England. Before the war it seemed paradoxical that so many New Englanders were vaccinated before going to countries in Europe that were free of smallpox, yet never gave a thought to vaccination before an extended motor trip along the St. Lawrence River, or to some states in the northwest where vaccination was not yet compulsory and where smallpox continued to occur.[†] The severest types of smallpox are epidemic in North Africa, the Orient, India and Mexico, the milder forms occur in the West Indies, northern South America, South Africa and Canada. In recent years outbreaks in the United States and Great Britain have been of milder variety.⁵

IMMUNOLOGIC CONSIDERATIONS

An attack of either chicken pox or smallpox tends to confer a lasting immunity. Most people in New England have chicken pox in early childhood and thereby, with rare exceptions, remain immune

throughout life. A few people exhibit a strong natural immunity through childhood and contract the disease in later life. Occasionally a parent who has not had the disease in childhood contracts it in a severe form from a mild case in one of his children. It is therefore desirable to have chicken pox in childhood in order to establish an immunity. If for any reason it is advisable to ward off an attack, an intramuscular injection of 10 to 20 cc. of convalescent chicken-pox serum within five days of exposure is likely to be effective because the incubation period is thirteen to twenty days.⁶ This passive immunity, however, lasts only two weeks.

Since cowpox affords a cross immunity to smallpox, it is advisable that all persons be vaccinated in early childhood. Indeed, whenever the question of a diagnosis of smallpox arises, one of the first steps is to look for a vaccination scar. This, of course, is only circumstantial evidence, because one can have varioloid, which is a mild form of smallpox modified through vaccination.⁷ Another point is that the incubation period of smallpox is about twelve days. Thus, in the event of an exposure to smallpox a certain degree of protection can be achieved by immediate vaccination.⁸ If the subject has had a previously successful vaccination, the amount of antibody already there is increased by the repeat inoculation of cowpox virus.

Although the incubation period of smallpox averages twelve days, it varies from eight to twenty-one days. The severer the form, the shorter is the incubation period. Thus, in so-called "black" or purpuric smallpox (variola purpurica), in which the patient succumbs in the period of invasion, the incubation period is only eight days. In such a case, the appearance of petechiae is followed by hemorrhages and collapse; the patient becomes the color of a "dark prune"⁹ and dies before the vesicular stage gets under way. On the other hand, in alastrim, which is a mild form of the disease in unvaccinated persons, the incubation period may be twenty-one days. Alastrim is due either to a high resistance in the individual or to a low virulence of the virus.

PRODROMAL SYMPTOMS

In general it may be stated that prodromal symptoms are absent or slight in chicken pox and severe in smallpox. The fact is that since chicken pox usually occurs in childhood and is usually a mild affair, prodromes are rarely present. Occasionally a child has a high fever, vomiting and even a convulsion within a few hours of the time when the first chicken-pox lesions are noted. Again, there may

*Clinical professor of infectious diseases, Harvard Medical School, professor of clinical medicine, Boston University School of Medicine, chief, Haynes Memorial Hospital, Massachusetts Memorial Hospitals.
†The state laws of Arizona, California, North Dakota, Utah and Minnesota do not require compulsory vaccination.

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* do not require compulsory vaccination.

vulva or on the prepuce. Sometimes, when the patient's resistance is exceptionally low, there is bleb formation. The contents of the blebs is usually pinkish from extravasations of blood. In seriously undernourished or otherwise debilitated infants, this bleb formation with secondary infection may progress to actual gangrene.¹⁰

The course of chicken pox, then, is usually two or three days of fever accompanying the eruption of vesicles, which continues over a period of two to five days. The scabs may come off in a week, but often they cling to a tough central root for two weeks or even longer. During the scab stage the patient is up and about.

The protracted course of events in smallpox consists of the severe and prolonged prodromes, followed by a brief period of lowered temperature and relative comfort. The first signs of the eruption then appear, usually during the third or fourth day of the acute illness, but in some mild cases as late as the seventh day. In general, all the lesions can be said to come out together, and thus tend to be at the same stage. This statement needs qualification, in the first place, because the lesions frequently appear twenty-four hours earlier on the face than elsewhere; and in the second place because in a given area one may find lesions in different stages of development.¹⁰ Thus, the statement that lesions in a given area tend to be at the same stage must be taken not as a reliable rule but merely in relation to the wider variation seen in chicken pox. The lesions begin as macules that last twenty-four hours. After this there may be another twenty-four hours in which they have a shotty feel, but as has already been stated, this is by no means always present. Then come firm, walled, umbilicated vesicles that at the end of twenty-four to seventy-two hours become opaque pustules. A sensation of burning in the skin often accompanies this eruption. The fever, which has been slowly mounting through the vesicular stage, rises abruptly with the pustular stage. The pustules remain for four to six days and then turn into crusts and scabs. These often remain a week or two, and as they come off they leave red pits that at the end of several months become white pitted scars. In the mildest forms of smallpox, however, there is often no scarring.

The distribution of the lesions tends to be centrifugal, and they are especially numerous on the face and forearms and below the knees. In these areas they tend to become confluent and all are much the same size. This confluence of the lesions brings about another feature of smallpox — namely, edema. The swelling along with the eruption may distort the face beyond recognition. The eyelids are so swollen that they do not open. The wrists, forearms, ankles, palms and soles may also be so swollen as to cause actual pain in conjunction with the burning sensation in the pustules.

The smallpox lesions also attack certain mucous

membranes, as is the case in chicken pox, but they do so more extensively. Instead of a few spots on the palate there may be numerous lesions there as well as on the buccal mucous membrane and tongue and over the posterior pharyngeal wall. Even the larynx may be involved. These lesions of the mouth and throat can be so painful that they make swallowing almost impossible. Furthermore, they give rise to a most repulsive halitosis. Lesions may also occur in the nose, on the palpebral conjunctivas and on the vulva.

Over any area where there is irritation of the skin surface, such as that from a hatband, collar, shoulder strap, waistband, belt or garter, the lesions are likely to show well demarcated confluence. Faller¹⁶ has gone at length into this selectivity of smallpox lesions for irritated parts of the skin. He draws attention to the fact that the lesions tend to be more marked about a scar and over bony prominences. He states that there are fewer lesions on a scalp that is protected by plenty of hair than on a bald area. He emphasizes the axilla, which is a favorite spot in chicken pox, but in which relatively fewer lesions are found in smallpox. This, he says, is particularly true of the apex of the axilla, which is so often involved in chicken pox but rarely in smallpox. He adds that, in general, smallpox tends to avoid the flexures of the skin more than does chicken pox. A readiness for lesions to appear where there is solar, thermal or mechanical irritation is present in both diseases but is more marked in smallpox. Gunn¹⁷ remarks that chicken pox shows a predilection for the sheltered parts of the body, such as the axillas and groins, whereas the converse is true of smallpox; and further, that chicken pox tends to avoid prominent parts and extensor surfaces. He also states that smallpox lesions are inclined to gather about "the sites of Mantoux and Schick tests where recent positive reactions have been obtained."

The blood count offers nothing reliable in the differential diagnosis — at any rate, not when it is needed — that is, at the onset of both diseases, in mild smallpox and severe chicken pox. Marked variations in the findings of the later stages have been recorded. In purpuric smallpox, white-cell blood counts of 16,000 to 46,200 have been recorded.⁹ The pustular stage of smallpox is accompanied by a marked leukocytosis. It is important to keep in mind that the streptococcus is the common secondary invader of the pustule, and that therefore a leukocytosis is to be expected. The streptococcus may also be a secondary invader in chicken pox, but an elevated leukocyte count cannot be depended on as a guide in this. I have seen a case of severe chicken pox in an adult with an overwhelming streptococcal pneumonia and blood stream infection in which the white-cell count was 8000, with only 68 per cent neutrophils. Holbrook²⁷ states that in chicken pox there is apparently a strong stimulus to lymphocytic activity with an increase in plasma

cells. Hoffmann²⁸ found 3 to 10 per cent eosinophils in the first three weeks of smallpox, rising to 15 to 20 per cent in the fourth and sixth weeks, whereas in chicken pox the percentage of eosinophils was normal at first, rising later to between 4 and 10 per cent. Gradwohl²⁹ states that the blood picture of chicken pox offers no information of value, but that that of smallpox is one of hyperleukocytosis with many irritation forms and plasma cells and a regenerative shift on the fourth day. It is doubtful whether this information would be of much diagnostic importance in a severe case of smallpox, and in the mild cases the leukocyte count is often not affected in any way.³

There are several laboratory tests for smallpox, but they can hardly be said to be practical when one is confronted with a case that is suspicious.

Sensitization test. This requires that a rabbit be sensitized to cowpox vaccine over a period of two weeks, after which the belly is shaved and the fluid from the suspected vesicle or pustule is inoculated intradermally. Material from smallpox gives a positive reaction in twenty-four to forty-eight hours, whereas that from chicken pox gives no reaction. The rabbit can be used again during the next eight months.

Flocculation test³⁰ and complement-fixation reaction.^{31, 32} These tests also involve the use of hyperimmune rabbit serum. The latter is more sensitive than the former. Provided the serum is at hand, both tests can be read promptly. They are definitely specific, but the first is not reliable in the first week of smallpox.

Intradermal cowpox-virus test. Cowpox (vaccine) virus heated to 56°C. is injected intradermally. A positive reaction can be obtained in a case of smallpox if the disease is sufficiently advanced to give an allergic reaction. This test is of no value in a previously vaccinated person.

Paul test. A needle dipped in the contents of the suspected vesicle is used to scarify the cornea of a rabbit. In smallpox, minute vesicles appear in forty-eight hours and ulceration follows; material from chicken pox causes no lesions.

Chick-membrane test.³³ Inoculation of the chorioallantoic membrane of a chick embryo with fluid from a smallpox vesicle gives a characteristic recognizable pox within forty-eight to seventy-two hours; no reaction occurs from chicken pox.

There is one situation that is exceedingly rare but that is worthy of mention — namely, concurrent chicken pox and smallpox. Schamberg¹⁸ reports such a case. More recently O'Connor³⁴ has described a case in which smallpox began six days after chicken pox.

* * *

There is no single feature, aside from specific laboratory tests, that can be relied on under all conditions to differentiate chicken pox and smallpox. The complete picture must be carefully studied. The patient, with the arms raised above the head, must be looked over from scalp to sole. Then the lesions must be closely examined. The rate and the manner of maturation of the lesions must be taken into consideration. Laidlaw³⁵ has pointed out the importance of realizing how mild smallpox can be. Wanklyn³⁶ has warned of the danger of relying too much on the presence or absence of "umbilication, shottiness, palatal and buccal lesions, lesions on the sole of the foot, cropping and uniloculation." Schamberg¹ has drawn

attention to the fact that in chicken pox one may find one or more lesions resembling smallpox, and vice versa. Ronaldson and Kelleher¹⁰ have described the anomalous forms of chicken pox. Hill¹⁹ has depicted the variety of lesions that are occasionally visible during each stage of the smallpox eruption. Finally, Faller¹⁶ and Gunn¹⁷ have reviewed the peculiarities of distribution of the lesions in the two diseases, as well as their behavior under the influence of previous irritation of the skin.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 30011

PRESENTATION OF CASE

First admission. A thirty-two-year-old housewife entered the hospital because of epigastric pain.

The patient had been in apparent good health until about fifteen months before admission, four months after a normal delivery, when she developed severe midepigastric pain. The pain was gnawing, intermittent, lasted two or three days and was not related to or altered by the ingestion of food or soda or by bowel movements. It persisted. Four months before entry the pain became severer and more constant. It at first occurred either a week before or a week after the menses but later had no relation to them. She was seen in the Out Patient Department about one month prior to entry and a cervical dilatation was performed, without benefit. The pain became much worse, radiating around the left side to the middle of the back and being aggravated by motion. She was unable to sleep. There was no nausea or vomiting, but her appetite was poor. She had tarry stools and dysuria for several days early in the illness but had had no recurrence of these. There was a weight loss of 10 pounds during this period. The menses had always been regular, each period lasting five days.

Physical examination showed a poorly nourished "wasted," pale woman looking older than her stated age. The heart and lungs were normal. There were marked tenderness and voluntary spasm in the midepigastrium, and slight tenderness in the suprapubic region, without spasm. Some costovertebral angle tenderness was elicited on both sides. Pelvic examination showed a lacerated, eroded, tender cervix; there was considerable odorless creamy discharge. The uterus was of normal size but extremely tender. The left ovary was not palpated. The right was not remarkable.

The blood pressure was 90 systolic, 60 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 4,700,000, with 60 per cent hemoglobin. The white-cell count was 11,400, with 45 per cent neu-

trophils, 47 per cent lymphocytes, 5 per cent basophils and 3 per cent monocytes. The urine was negative. A blood Hinton test was negative. The nonprotein nitrogen was 16 mg. per 100 cc. The blood protein was 6 gm. per 100 cc., the chloride 91.5 milliequiv. per liter, and the sodium 137 milliequiv. per liter. Repeated stool examinations were guaiac positive. No stool culture was reported.

A gastrointestinal series was negative, as was a barium enema. A small-bowel enema through the Rehfuß tube showed slightly slow passage of the fluid filling the jejunum and the greater portion of the ileum. There was a delay in the passage of fluid at the junction of the middle and lower thirds of the right ileum on the right side of the abdomen. There was slight ballooning, for which no anatomical basis could be demonstrated. The barium entered the cecum at the end of thirty minutes, and half an hour later, the ileum, cecum and colon were filled with barium. No localized areas of narrowing or any other defects were seen. Proctoscopic examinations were negative but seemed to reproduce the pain. The temperature occasionally rose to 100°F., but the pulse and respirations were normal. A pre-operative diagnosis of endometriosis was made, and a hysterectomy and appendectomy were performed. Exploration of the entire abdomen and gastrointestinal tract was said to have shown no abnormalities. The spleen was twice the normal size.

Except for an occasional rise of temperature to 99.8 or 100°F. the postoperative course was uneventful. The epigastric pain had completely disappeared. Pathological examination of the uterus and the appendix showed no abnormality. It was deemed advisable to transfer the patient to the Medical Service for further study and determination of the cause of the positive guaiac test on the stool, but she refused and was discharged on the twenty-eighth hospital day.

Second admission (nine months later). After discharge the patient remained free from pain for about a month. She then noted a gradual return of symptoms, with the development of constant upper abdominal pain that occasionally radiated to the left thigh. On one occasion she had a severe attack of pain accompanied by chills and a bout of vomiting. The nature of the vomitus was not known. Her appetite became poor. There had been urinary incontinence and dyspareunia since operation. She had lost 19 pounds of weight.

Physical examination showed an emaciated, rather anxious woman complaining of mild abdominal pain. The heart and lungs were normal. The abdomen was tense, with mild generalized tenderness more marked in the upper half. The liver was palpated two fingerbreadths below the costal margin. There was questionable costovertebral-angle tenderness bilaterally. Pelvic examination showed tenderness throughout. There was marked generalized muscle wasting of the extremities.

*On leave of absence.

The blood pressure was 95 systolic, 70 diastolic. The temperature was 99.8°F., the pulse 90, and the respirations 20.

Examination of the blood showed a red-cell count of 5,000,000, with 12.5 gm. of hemoglobin. The white-cell count was 7200, with 80 per cent neutrophils. The platelets were normal. The neutrophils showed a shift to the left. The urine was negative. The stools were guaiac positive. A cephalin flocculation test was +++ in twenty-four hours and ++++ in forty-eight hours. A van den Bergh test was negative. The blood protein was 6 gm. per 100 cc. A bromsulfalein test was negative. X-ray films of the chest were negative. The spleen did not appear enlarged. An intravenous pyelogram was negative. A Graham test showed a normally functioning gall bladder; many minute radiolucent shadows, with a dense ring about them, were present within the shadow of the gall bladder, which had the appearance of calculi. X-ray examination of the gastrointestinal tract was handicapped because of the refusal of the patient to take more barium. There was a questionable thickening of the gastric mucosal rugae, but no ulceration or narrowing could be seen. Considerable pylorospasm was noted, but the duodenal cap, the second and third portions of the duodenum and the upper jejunum filled normally. There was pressure on one of the loops of jejunum by a mass arising out of the pelvis, which might have been the distended bladder. The bones were normal.

The patient continued to complain of epigastric and considerable back pain. She was placed on a high-calorie, high-vitamin diet but was unable to take much food by mouth "because it was not Portuguese style." During the third hospital week she had several attacks of severe epigastric pain radiating through to the back. The temperature ranged between 100 and 100.5°F.; the pulse and respirations were normal. Her condition improved but slightly during the fourth week, and she was discharged home on a high-calorie, low-fat, high-vitamin diet, to return at a later date for cholecystectomy.

Third admission (one month later). Following discharge the patient continued to have severe epigastric pain and nausea but no vomiting. Her appetite remained poor. There was some additional weight loss.

Physical examination showed a markedly emaciated woman in acute distress. There were tenderness in the right upper quadrant, voluntary abdominal spasm and slight right costovertebral-angle tenderness.

The blood pressure was 90 systolic, 60 diastolic. The temperature was 100°F., the pulse 100, and the respirations 20.

Examination of the blood showed a red-cell count of 4,100,000, with 60 per cent hemoglobin. The white-cell count was 10,400, with 70 per cent neutro-

phils; the smear showed a shift to the left, with many band forms. The urine was negative. The stools were guaiac positive.

The patient was given several transfusions and intravenous injections of fluid, with chills and fever following each transfusion. Proctoscopy was again negative. The temperature during the first two weeks ranged about 100°F. On the fourteenth day the temperature rose to 104°F., and the pulse to 150; the respirations were normal. Examination showed diffuse tenderness with spasm in the right upper quadrant. Sigmoidoscopy two days later was negative.

On the eighteenth hospital day the patient developed marked abdominal distention, vomiting and diarrhea. The temperature ranged between 100 and 104°F. Examination showed marked abdominal distention with tympany. There was diffuse tenderness without any rebound. High-pitched peristalsis of an obstructive character was audible, with periods of hyperactivity and silence. There was pain in both shoulders. X-ray films showed several loops of small bowel that were distended with gas, but no free air was seen in the peritoneal cavity. The white-cell count was 15,800. The urine showed a + test for albumin, and the sediment contained many white cells. A Miller-Abbott tube was passed but could not be manipulated beyond the pylorus.

On the twentieth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. J. H. MEANS: This is a case of some complexity, and of extraordinary interest as a problem—a tough problem, it seems to me—in differential diagnosis. The outstanding feature is that this syndrome was characterized by extremely persistent and at times apparently severe midepigastric pain that was peculiar in its lack of relation to any other bodily function and by gradually increasing fever and weight loss. The only clue that has been given concerning its nature is that it was reproduced by doing a proctoscopy. Whether that is of importance I do not know; but it did interest me. This affair had been progressing for two years and was relieved by hysterectomy but for only a month. It is interesting that the pathologist apparently found the uterus to be normal. The appendix was taken out at that time, so that is out of the picture, and finally the story ends with an attack of acute intestinal obstruction that required an emergency operation. It does not sound like a long-planned operation. I suppose it led to a diagnosis.

This case was thoroughly studied, and there is a great deal of material here for digestion. I made a list of positive findings, and there also are a great many significant negative ones. The pain itself I put first. I am much impressed with the one attack of tarry stools and the fact that every stool thereafter was guaiac positive. We cannot escape that.

She had been constantly losing blood in the stool. She had progressive weight loss, emaciation and hypochromic anemia. I shall ask the radiologist to interpret the films later, but it appears that the radiologist found some evidence of stasis, at least in the small bowel. There was questionable enlargement of the liver. The patient apparently had gallstones. The positive cephalin flocculation test might go with an enlarged liver, suggesting some parenchymatous disturbance in the liver or disturbance in liver function. In looking the record over very thoroughly, it seems to me that we have to find a focal lesion somewhere as an explanation for the picture, and I think it is reasonable to assume that it was below the diaphragm.

The case in favor of the gastrointestinal tract as the location is the strongest, and yet there are some things that bother me about attributing it to the gastrointestinal tract. There is this business about the pelvis. I am disturbed about the backache, which could be due to the gastrointestinal lesion. One can have backache in peptic ulcer, so that the backache could be of alimentary origin. There was pain in various places, — in the upper quadrant, in the suprapubic region and once in the left hip, — although usually it was in the midepigastrium. It was a bizarre type of pain.

I thought of disease in the kidneys, but there was a negative pyelogram and the urine was negative until just before operation, when it had some pus in it as a part of the acute picture. I thought about the pancreas, but I cannot explain all the picture on the basis of a pancreatic lesion. Nor can I explain it all on the basis of the gall bladder. She could have had liver disease. The liver is said to have been enlarged, but that is questionable. The cephalin flocculation test was suggestive of some disturbance in liver function, but the other tests were negative. The liver I shall leave on the periphery, as a possible but not probable locus of the lesion.

I thought of spinal disease, psoas abscess and things of that sort and abandoned them all, and came back to the gastrointestinal tract as the probable location of the lesion. The gastrointestinal tract was thoroughly studied. Everything was negative except the small bowel, so I was forced to conclude that the lesion was in the small bowel, although small-bowel lesions other than duodenal are rarer than those of the large bowel or stomach. At this point I shall ask the radiologist to give what help he can.

DR. MILFORD SCHULZ: Most of these films are just confirmatory of all these negative examinations.

DR. MEANS: Is there anything wrong with the spine, such as metastatic disease?

DR. SCHULZ: There is no gross lesion in the bones.

These are the films that we made at the time of the examination of the small bowel. The delay in the passage of barium through the small bowel was

a fluoroscopic observation. The small-bowel pattern is not unusual, and there does not seem to be a mass displacing it. Of course it is notorious that lesions in the small bowel are overlooked, or not demonstrated in x-ray examinations. Meckel's diverticulum and things like that are rarely found.

This is the film made on the second admission. The mass could well be a full bladder. On the other hand the bowel is not entirely filled and it is impossible to say whether or not an abdominal mass is present. The rest of the films are confirmatory of what has been said.

DR. MEANS: You cannot tell me with confidence that there is obstruction in the small bowel?

DR. SCHULZ: There is no obstruction. The barium enters the colon without any evidence of dilatation of the small bowel. The small bowel pattern itself seems to be normal.

DR. MEANS: Can you say that there was stasis in the small bowel that was pathologic?

DR. SCHULZ: Not from these films. That probably was the observation of the man who did the fluoroscopy and administered the small-bowel enema.

DR. MEANS: I have to go on what evidence I can get. Do you think I can assume that the fluoroscopist's opinion that there was delay in the small bowel is something to be taken seriously?

DR. SCHULZ: I do not know what to make of the impression of hesitancy in the passage of barium in the small bowel. I am willing to grant that it was a reliable observation.

DR. WILLIAM B. BREED: Does not one of these pictures show dilatation of the small bowel?

DR. SCHULZ: Yes; but the film was taken just before surgery and shows obstructed small bowel, distended with gas.

DR. MEANS: The patient had intestinal obstruction by that time. Can you locate it? Was it in the small bowel or large bowel?

DR. SCHULZ: I suspect that it was in the small bowel. The loops that you see here are jejunal. There may be a small amount of air in the colon, but the colon is not correspondingly dilated.

DR. MEANS: It seems to me quite evident that the patient had intestinal obstruction at the end. Why did she have it? Of course I could go through all the causes of acute intestinal obstruction. There is no need to do that, however, and I shall consider only those things that fit with the rest of the total picture. When the surgeons performed the hysterectomy, they carefully explored the abdomen and found nothing pathologic. Furthermore, a gastrointestinal series, special small-bowel films, barium enemas, pyelograms and cholecystograms, all were negative, except that gallstones were found.

Regarding differential diagnosis, first of all there is this matter of endometriosis. I bring that up because it was brought up by the service. I gather that the diagnosis was never confirmed. Could it be endometriosis? I do not know a great deal about

this disease but the textbooks state that it may involve the bowel, rarely the small bowel. Indeed it occasionally gives rise to bleeding of the small bowel, although the lesion generally does not extend through to the mucosa. So I think that endometriosis of the small bowel is extremely unlikely.

I thought of regional ileitis, of course, because it is a disease of the small bowel and I had rather sold myself the idea that the trouble was in the small bowel. Regional ileitis I rule out because the radiologist found no evidence of characteristic sort, and because the patient did not have, according to my interpretation, recurring attacks of incomplete obstruction, which are usually found in regional ileitis.

I thought of tuberculosis of the bowel. It can occur in the small bowel, but it usually involves the cecum as well, shows on x-ray study, and is usually secondary to tuberculosis elsewhere. I shall dismiss it.

A case of a peptic ulcer in a Meckel's diverticulum was presented here some time ago; that intrigued me a little bit. Such lesions do bleed. They are peptic ulcerations — apparently a Meckel's diverticulum often contains some gastric mucosa, which may produce a peptic ulcer. This patient's pain was high, whereas I should expect it to be around the umbilicus in a lesion of Meckel's diverticulum; but we cannot have everything just as we want it in these conferences. Therefore, I think that a peptic ulcer in a Meckel's diverticulum should be kept as a possibility. We have to find some lesion that explains the back pain and persistent bleeding. Those seem to be the things that are crying more for explanation than anything else. These two symptoms seem to be the salient features. A lesion in the small bowel that was bleeding persistently would result in anemia and interference with nutrition, so that the patient developed a progressive wasting disease. I suppose peptic ulcer of a Meckel's diverticulum could do these things. It does occur in adults but is commoner in children.

The matter of cirrhosis has to be mentioned. I do not know whether or not the liver was enlarged. The abdomen had been looked into, and seemed to be perfectly normal. I do not believe that she had cirrhosis, but it has to be mentioned in the differential diagnosis because it could have given rise to gastrointestinal bleeding. But the bleeding was different in character than what one gets in cirrhosis. It is not apt to be a steady oozing, as it was in this case. She had one bout of massive bleeding in the beginning, to be sure, but generally it was steady oozing, which is not characteristic of cirrhosis. The positive cephalin flocculation test indicates that perhaps the liver was "sick." No varices were demonstrated by x-ray, but the radiologist does not always disclose varices. Another source of varices is splenic-vein thrombosis, but I cannot square this picture with that condition. Cirrhosis should be mentioned but is unlikely.

I suppose that the gallstones could have produced the pain, although it certainly was far from typical. I do not see how gallstones could have produced the bleeding, therefore I conclude that they had nothing to do with the picture.

Next, one has to think of all the tumors of the small bowel that might ulcerate within the lumen and cause such a picture as this. There are the benign ones — fibromas, myomas, angiomas and lipomas. Then there is carcinoma, and finally lymphoma. At this point I ran out of ideas. I shall limit my differential diagnosis to the conditions mentioned. Perhaps the joker will be that the lesion was not in the small bowel. What was this thing in the pelvis? Was it bladder? It was not uterus. I do not know what it was. The pelvic examination, as I remember it, was negative.

Of all these various things that I thought of, I believe that lymphoma is the most probable. I think that it could do everything that is present in this case. It even could cause this backache. There might be retroperitoneal involvement by a lymphomatous process that no one could demonstrate. Costovertebral tenderness could have been due to involvement of the kidneys. I know that lymphoma can involve the small bowel, giving a localized tumor that often ulcerates and bleeds. It can also cause acute intestinal obstruction. Therefore I shall put lymphoma first. I think that the other things that I mentioned are possibilities. I should like to ask the pathologist whether lymphoma ever involves the adrenal glands and produces the picture of Addison's disease.

DR. BENJAMIN CASTLEMAN: It may involve the adrenal glands when the lymphoma is generalized. I have never seen it limited to the adrenal glands or produce the symptoms of Addison's disease.

DR. MEANS: I was intrigued by the low blood pressure, but I do not believe that it is important. There is no mention of pigmentation, and the gastrointestinal picture was not that seen in Addison's disease. There was a low blood chloride, but a normal blood sodium. I mention it but I do not believe that the patient had Addison's disease.

DR. BREED: I recall your discussing the case of a patient who had a hole in the diaphragm. This picture is certainly characteristic of a diaphragmatic hernia, and with the usual epigastric pain and bleeding, I wonder whether the x-ray man missed it and whether the exploring surgeon missed it. I just toss it in as a thought.

DR. MEANS: It is an interesting suggestion and had not occurred to me. I assume that they ruled out all these things because they look routinely for diaphragmatic hernia, certainly in cases of obscure pain. Diaphragmatic hernia certainly gives rise to pain and to bleeding. It might be considered. The way I interpret this picture, however, is that they found nothing at laparotomy, because at that time the lesion was within the lumen.

DR. CASTLEMAN: Would you not see something in the film of the chest if it were a diaphragmatic hernia?

DR. MEANS: The case that Dr. Breed refers to was interpreted roentgenologically as hydropneumothorax, which it was not. It was a stomach that filled the entire chest and was half filled with fluid.

A PHYSICIAN: How about partial intussusception that released itself and just gave enough symptoms?

DR. MEANS: I thought of intussusception as a possibility, but did not go into the actual nature of the acute intestinal obstruction just before the last operation. Any lesion within the lumen of the small bowel may set up intussusception and cause obstruction, I suppose. I am sure that the whole story, from start to finish, is not that of intussusception.

DR. REED HARWOOD: Did the mass in the pelvis, thought to be a full bladder, persist, or did it disappear?

DR. A. G. BRENIZER: The mass was not palpated on physical examination until the last entry. It felt as if it might be loops of bowel matted together, but it was not definite and was not included in the record for that reason.

DR. FLETCHER H. COLBY: How about mesenteric thrombosis? It would account for the last episode.

DR. MEANS: I was working harder on the two-year story than on just what happened before laparotomy. Mesenteric thrombosis may have occurred, but I do not see how it would hook up with the two-year story.

DR. CASTLEMAN: Dr. McKittrick, will you tell us about your operative findings?

DR. LELAND S. MCKITTRICK: It is too bad we did not have Dr. Means on the service. We are not proud of our diagnosis.

The patient had gallstones, but everybody thought that they could not conceivably give the picture that she had and we transferred her to the Medical Service for complete study. The mass in the lower abdomen did not disappear after the bladder was catheterized. We were disturbed about the persistently positive guaiac tests on the stools. We thought that the lesion was in the small bowel. We did not give quite the careful consideration in differential diagnosis that Dr. Means has, so we did not do well. We thought that the diagnosis lay between tuberculous peritonitis, with involvement of the bowel, and a regional enteritis. An operation was performed on that basis, and also with the assumption that recent perforation had occurred, with abscess formation. She had a large perforation and a walled-off abscess containing 50 to 60 cc. of small-bowel contents. We removed a segment of friable, open, small bowel and did an anastomosis, without knowing at the time what the lesion was. One of the members of the Pathology Department looked at the specimen, but even then it was difficult to be sure just what the lesion was; that is where we left it.

CLINICAL DIAGNOSIS

Tuberculosis of small intestine, with tuberculous peritonitis?
Regional enteritis?

DR. MEANS'S DIAGNOSES

Lymphoma of small intestine.
Acute intestinal obstruction.

ANATOMICAL DIAGNOSIS

Malignant lymphoma, lymphoblastic type, of small intestine, with perforation.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The fresh specimen contained many matted loops of hemorrhagic small bowel covered with a fibrinous exudate. When these were opened we were able to find a stenotic lesion about 3 cm. long in about the midportion of the specimen. The tumor was submucosal. Microscopic examination confirmed Dr. Means's diagnosis of lymphoma of the small bowel, which had perforated. We classified it as a lymphoblastic type of lymphoma. The regional lymph nodes, as is usual in isolated lymphoma of the gastrointestinal tract, showed no evidence of disease.

The patient is now convalescing.

CASE 30012

PRESENTATION OF CASE

A sixty-year-old man, a schoolteacher, was admitted to the hospital because of increasing dyspnea and peripheral edema of several weeks' duration.

Fourteen years before entry the patient noted shortness of breath and rapid heart action. He consulted a physician and was found to have auricular fibrillation. He was given digitalis, which he took regularly thereafter. Ten years before entry he stopped taking the drug for a brief interval, but returned to it because of the reappearance of dyspnea. Throughout the fourteen years he carefully regulated his existence. Two years before entry he consulted a cardiologist because of dyspnea. He was given subcutaneous diuretics, and voided 6 to 8 liters of fluid, with much relief. On two subsequent occasions similar diuresis was employed. About a year before entry he began to require more pillows for sleeping, and shortness of breath troubled him in his work. Eight weeks before entry he had an attack of grippe characterized by slight fever, malaise and a cough which, though slight, produced small amounts of sputum tinged with bright-red blood. Following this, the legs, scrotum and abdomen became swollen, and shortness of breath in-

creased. There was marked oliguria without response to diuretics.

The remote history and family history were irrelevant.

Admission examination showed a well-developed man sitting up in bed with marked dyspnea. There was advanced edema of the legs, sacrum and back. The face and extremities showed a deep-purple cyanosis. The veins over the neck and extremities were distended. There was questionable dullness with moist rales over both pulmonary bases. The heart was much enlarged, extending 10.5 cm. to the left of the midline in the fifth interspace. A loud systolic murmur was heard at the apex, with a soft blowing diastolic murmur along the left sternal border and a questionable diastolic murmur in the mitral area. There was auricular fibrillation, with an apical rate of 93 and a radial rate of 78. The abdomen was edematous, with the liver edge five fingerbreadths below the costal margin. The blood pressure was 128 systolic, 100 diastolic.

Examination of the blood showed a red-cell count of 5,900,000, with 18.1 gm. hemoglobin, and a white-cell count of 12,200, with 83 per cent neutrophils. The nonprotein nitrogen was 42 mg. per 100 cc. The urine showed a +++ test for albumin and a specific gravity of 1.022; there were a few red and white cells in the sediment.

The patient was given diuretics, and Southey tubes were inserted. In the course of eleven days he lost 37 pounds of fluid. The drainage incision in the left foot became infected, and a cellulitis developed.

During the third week in the hospital the patient began to lose ground. He developed purpuric areas on the left foot and right hand, and became more and more cyanotic. The cellulitis of the dorsum of the left foot spread widely but did not extend past the lower leg. *Staphylococcus aureus* and a beta-hemolytic streptococcus were twice cultured from the foot. A blood culture was negative. Terminally, bronchial breathing appeared at the left base and the patient became mentally confused. He died on the thirty-fifth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. DERA KINSEY: Obviously this patient's immediate problem was marked congestive heart failure. From his history we know this congestive failure began fourteen years before entry and may have been precipitated by the onset of auricular fibrillation. The kind of heart disease the patient was suffering from is not so obvious because we have no record of the physical findings until the terminal illness, at which time there was marked cardiac enlargement with both right and left ventricular failure, as indicated by dyspnea, engorgement of the neck veins and liver, and edema of the lower extremities, sacrum and back.

It is impossible definitely to evaluate the murmurs

described in this completely failing heart, since all of them might have been due to dilated and distorted valvular rings secondary to dilatation and hypertrophy of the heart. If the questionable diastolic murmur was really heard in the mitral area, however, we must strongly suspect rheumatic heart disease with mitral stenosis. It is interesting to note that the admission blood pressure was 128 systolic, 100 diastolic. This high diastolic pressure suggests that the patient previously had had hypertension, although there is no past history of it or of angina. We should like to have had further studies, such as fundi examination, electrocardiograms, x-ray films and so forth. Nor was there a previous history of rheumatic fever. The patient might well have had both rheumatic heart disease, with mitral stenosis, and essential hypertension since these two conditions are not uncommonly found in the same patient. He probably did not have beriberi, thyrotoxicosis or congenital heart disease because of the long duration and the age and lack of history. The orthopnea and dyspnea that the patient experienced in the beginning of his illness might have been due to acute ventricular failure as a result of hypertension or pulmonary edema as the result of mitral stenosis and precipitated by the sudden onset of auricular fibrillation.

This patient got along fairly well with his carefully planned existence until he developed a complication. Most people with congestive heart failure die of a complication rather than of the congestive failure per se. The commonest complication in congestive failure is pulmonary infarction, and second, pulmonary infection. Often the two appear together. The onset of this patient's terminal illness was probably due to pulmonary embolism and infarction. We may suspect this because of the so-called "attack of grippe," which was characterized by fever, malaise and the blood-tinged sputum. We know that chest pain is not always present with infarction. Further evidence of infarction are the mild polycythemia and the elevated hemoglobin level, both of which are consistent with cor pulmonale, which is associated with pulmonary infarction. It is unusual to note cyanosis to the extent this patient had in congestive failure alone. Pulmonary infarction in congestive heart failure is usually due to an embolus from the leg vein. It may also come, however, from the right side of the heart in the presence of mitral stenosis. In this patient, there is no indication by physical findings to the source of the emboli. The infarction might also have been due to local pulmonary thrombosis. The albumin and increased nonprotein nitrogen might have been caused by circulatory failure or, still more likely, by vascular nephritis and circulatory failure. The patient no doubt had a terminal bronchopneumonia.

My diagnoses are hypertensive coronary heart disease, questionable rheumatic heart disease with

mitral stenosis, pulmonary infarction with terminal pulmonary infection, cor pulmonale and cellulitis of the foot.

CLINICAL DIAGNOSES

Rheumatic heart disease with mitral stenosis, slight aortic involvement (regurgitation) and tricuspid regurgitation (?).
Local infection and gangrene: left foot.
Congestive failure.
Auricular fibrillation.

DR. KINSEY'S DIAGNOSES

Hypertensive coronary heart disease.
Rheumatic heart disease, with mitral stenosis?
Pulmonary infarction, with terminal pulmonary infection.
Cor pulmonale.
Cellulitis of foot.

ANATOMICAL DIAGNOSES

Rheumatic heart disease.
Endocarditis, chronic rheumatic, with aortic and mitral stenosis.
Mural thrombi: right and left auricles.
Chronic pulmonary thrombosis (? embolic).
Pulmonary endarteritis.
Cor pulmonale.
Cirrhosis of liver, cardiac.
Hemorrhagic bronchopneumonia: right lower lobe.
Hydrothorax, slight, right.
Sepsis: left foot.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The post-mortem examination showed severe chronic rheumatic heart disease with mitral and aortic stenosis. The heart was markedly hypertrophied, weighing 700 gm. With severe mitral disease one expects some degree of hypertrophy of the right ventricle, but in this case the right wall measured 11 mm. in thickness, or almost four times the normal, so that some additional factor must have been superimposed on the mitral stenosis. The major branches of the right and left pulmonary arteries were almost completely occluded by adherent organized thrombi. The smaller branches showed atherosclerosis but no thrombi. Whether these thrombi originated as emboli and then increased in size by superimposed thrombosis is anyone's guess. I personally believe they began as emboli, which may have arisen from the right auricular appendage, which was filled with thrombus, or from the deep leg veins. Microscopically there was marked intimal atherosclerosis of the small arteries. There certainly was enough cutting down of the pulmonary circulation to produce the cor pulmonale. There were no infarcts, apparently because these thrombi or emboli were in the larger vessels and had developed slowly enough to allow for collateral circulation.

Other findings were hemorrhagic bronchopneumonia in the right lower lobe, cardiac cirrhosis of the liver and a mural thrombus in the left auricular appendage as well as in the right. The coronary arteries showed only slight sclerosis.

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DYSENTERY

For many centuries, dysentery has been a serious problem in times of stress, such as famine and war.¹ Epidemics during World War I, particularly that during the campaign at Gallipoli, are well documented, and accounts of outbreaks during the German invasion of Poland in 1939² and in the more recent campaign in the Middle East³ demonstrate that this epidemic disease still stalks armies. More important, however, is the fact that troops of the United Nations are now fighting or stationed in notoriously bad endemic areas—West and North Africa, several islands in the South Pacific, India, the West Indies, and Central and South America.

The commonest types of dysentery are caused by

a variety of bacteria and by an ameba, *Endamoeba histolytica*, but bacillary dysentery is by far the more important and serious. Other diseases, such as schistosomiasis, kala-azar and malaria, can cause dysentery, but these types seldom assume epidemic proportions.

In a recent and important review of bacillary dysentery, Weil⁴ has pointed out the accumulation of a considerable amount of new information during the last fifteen years, much of which has not found its way into textbooks and into practical application in medicine and public health. This fact is regrettable because of the continued occurrence and relatively high incidence of this disease in many parts of the world and in certain areas of this country.

According to the *Public Health Reports*, the reported cases of dysentery in the United States in 1940 were as follows: amebic dysentery, 2991 cases; bacillary dysentery, 19,152 cases; and undetermined, 1484 cases. Although mortality figures are distorted because many cases are unreported, the mortality of 17.8 per cent among 79,042 reported cases of bacillary dysentery from 1933 to 1937 gives an idea of the importance of the problem in normal times in this country.⁵ The situation for Europe and Japan is somewhat similar, with comparable morbidity and mortality figures. Obviously these figures cannot be applied to tropical countries, where everyone faces the likelihood of infection.

In both types of dysentery, man is the source of organisms for the contamination of food and water. Cysts of *E. histolytica*, the infective stage of amebic dysentery, cannot withstand drying but they can remain viable in water from several days to approximately five or six months, depending on the temperature, the amount of bacterial growth and the concentration of suspended organic material.⁶ Dysentery bacilli can withstand drying for twenty to twenty-five days⁷ and can live for variable lengths of time in flies, ants, milk and water. Thus, healthy carriers of *E. histolytica*, chronic cases of amebic dysentery, and convalescent or contact carriers of dysentery bacilli are of the utmost significance to the public-health official and to the medical officer in the armed forces.

In New York City, studies of 6324 healthy per-

sons for dysentery bacilli gave an incidence of 2 per cent, and the figure rose to 3.2 per cent when 1659 persons were examined in New Mexico, Georgia and Puerto Rico.⁴ Hurst and Knott⁸ state that not less than 1 per cent of all patients with Flexner infections become permanent carriers. The incidence and persistence of infections in institutions where the disease is endemic can be as high as 80 per cent. In troops fighting in endemic areas, the problem is a serious one and campaigns can easily be disrupted because of the occurrence of an epidemic.

Among a civilian population, modern methods of sanitation effectively control epidemics of bacillary dysentery in normal times, but poor housing conditions, too rapid growth of towns and cities, and crowding of defense workers cause the best laid systems of sanitation to break down in times of war. The present war of rapid movement minimizes the dangers in an army to some extent, but the problem of supplying food and water in tropical areas is potentially a great source of danger.

A correct laboratory diagnosis is essential for the clinician to verify the disease that confronts him. Emphasis should be placed on the facts that dysenteric infections can assume a variety of forms and that not all dysentery is caused by amebas or bacilli. Only after a thorough search of the feces for pathogenic bacteria and protozoa, and a blood examination for malarial parasites if the patient comes from an endemic area, is the clinician in position to treat the case properly and to control the spread of infection. Under field conditions, this procedure is not only impractical but often impossible for medical officers, and the only available procedure is a therapeutic test—quinine or atabrine for malaria, carbarsone or yatren for amebic dysentery and sulfonamides for bacillary dysentery. Of the last, sulfathiazole and sulfaguanidine have been given the most extensive trials; however, after sulfathiazole, fecal samples may become positive again for dysentery bacilli, and sulfaguanidine appears to be more effective against the Flexner bacilli than in Sonne infections. From the many and varied recent reports on the treatment of bacillary dysentery, it is quite apparent that the trials have been too few to properly evaluate sulfonamide drugs. The opportunity provided by

the present emergency will at least provide numerous occasions to prove or disprove their efficacy.

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CANCER REMEDIES

EVEN in the midst of war, purported cancer remedies continue to appear. The most recent flurry is concerned with an English preparation known as "H 11." This is an extract of urine that is supposed to have tumor-inhibiting properties. As usual, the earlier reports appeared promising but the later give little, if any, hope that the substance is of value.

The material, prepared by Thompson,^{1, 2} has been utilized by several groups for therapy of both human cancer and induced as well as spontaneous transplantable cancer in animals.^{3, 4} In one series of 51 advanced cases of cancer, 37 cases received dosages that might be regarded as sufficient for fair clinical trial.⁵ Among these, 11 died and the results were unknown in 5 cases. The longest period of survival was eighteen months. All the patients surviving, except two (who lacked biopsy proof of the presence of cancer) had some other form of therapy in addition to H 11. In none of the cases in which H 11 was used did the growth disappear. There was a suggestion of slight clinical improvement in some cases, but this has often proved to be misleading in evaluating remedies.

The evidence seems to indicate that this urinary extract is without value as a therapeutic agent in cancer.

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MEDICAL EPONYM

PARDEE'S SIGN

Harold E. B. Pardee (b. 1886) describes "An Electrocardiographic Sign of the Coronary Artery Obstruction" in the *Archives of Internal Medicine* (26:244-257, 1920). A portion of the article follows:

... It is hoped to show that obstruction of a branch of coronary artery is followed by a sign which is characteristic of this condition and is readily recognizable in the human electrocardiogram.

... The characteristic changes appearing a day or two after the obstruction are as follows: The QRS group is usually notched in at least two leads, and usually shows left ventricular preponderance. The T wave does not start from the zero level of the record in either Lead I or Lead 3, though, perhaps, from a level not far removed from it, and in this lead quickly turns away from its starting point in a sharp curve, without the short straight stretch which is so evident in normal records preceding the peak of the T wave. The T wave is usually of larger size than customary and accordingly shows a somewhat sharper peak. The T wave is usually turned downward in Lead 2 and in one other lead. Not all of these changes are to be found in every record, but enough of them are present to give it a characteristic appearance.

R. W. B.

WAR ACTIVITIES

PROCUREMENT AND ASSIGNMENT

FUNDS FOR RELOCATION OF PHYSICIANS

The following statement was recently released by the Bureau of Legal Medicine and Legislation of the American Medical Association.

* * *

Under the date of October 1, the President transmitted to Congress supplemental estimates for the United States Public Health Service amounting to \$4,427,550. It was contemplated that of this total \$1,000,000 would be used to supply medical care to civilians in critical areas. Such care, it was proposed, would be supplied in one of two ways: by the assignment of medical officers of the Public Health Service to such areas to treat civilians under a fee schedule agreed on by the Public Health Service and the state department of health or by inducing civilian physicians to relocate to the critical areas by paying them a relocation allowance of \$250 a month for three months, as well as moving expenses.

These estimates were referred to the House Committee on Appropriations, which refused to include in the First Supplemental National Defense Appropriation Bill for 1944 (H. R. 3598) the requested funds for supplying medical care to the critical areas and justified its action as follows:

The committee in rejecting the Budget request does not minimize the need or the seriousness of the situations which exist. It does hesitate to inaugurate a program of this character with federal funds to provide direct medical attention to the civilian population with physicians paid by the federal government. The committee has the opinion that out of the co-operative efforts of the federal government, the medical associations, the state departments of health and the communities themselves, there will and should come a concerted and spontaneous effort to provide this need. Most of it is in war-industry areas, and it is inconceivable that such communities working with the industries, the affected population, and state and local authority, cannot inaugurate and maintain an adequate public-spirited program, financially sound, to serve this need. If the affected areas cannot and will not solve their local needs it may be necessary for the federal government

in the interest of the general public health to step in, but until then the committee feels that federal funds should be withheld under the contemplated procedure.

In the Senate, H. R. 3598 was amended, at the instance of Senator Russell, of Georgia, to authorize an appropriation of \$345,000 for use by the Public Health Service in providing medical care to civilians in critical areas subject to the following conditions and restrictions:

Provided, That the Surgeon General is authorized, on application of a municipality, county or other local subdivision of government duly approved by the state health department having jurisdiction over said municipality, county or other local subdivision of government, to enter into agreements with private practicing physicians and dentists under which, in consideration of the payment to them of a relocation allowance not to exceed \$250 per month for three months and the actual cost of travel and transportation of the physician or dentist and his family and household effects to the new location, such physician or dentist will agree to move to and engage in the practice of his profession in such area for a period of not less than one year: Provided, however, That no such contract shall be made with any physician or dentist unless such physician or dentist shall be admitted to practice by the state authority having jurisdiction of such new location: Provided further, That each such applicant subdivision shall contribute \$100 to the total cost of such relocation allowance, travel and transportation costs of each such physician or dentist and his family obtained by said applicant.

The bill passed the Senate with this amendment in it. It will now be considered by a conference committee composed of representatives on the part of the House and on the part of the Senate, in an effort to adjust the differences in the bill as it passed the House and as it passed the Senate.

Copies of the *Congressional Record* for December 8, the date on which Senate action on the Russell amendment occurred, are being sent to each state medical society. This procedure is followed because of the extremely important discussion that preceded the adoption of the amendment, many senators desiring assurance that the amendment in no way involved the socialization of the practice of medicine.

MISCELLANY

AMERICAN COLLEGE OF SURGEONS

During 1943, the following physicians in Massachusetts, New Hampshire and Vermont were accepted as fellows of the American College of Surgeons:

Massachusetts: Matthew J. Bachulus, Longmeadow; Z. William Colson, Lawrence; Gordon Donaldson, Boston; Clifford C. Franseen, Newton Centre; Thomas A. Hathcock, Jr., Brighton; Paul C. Keleher, Woburn; James A. Lamphier, Brookline; David A. Latham, Chelmsford; Ernest H. Latham, N. Chelmsford; Timothy F. P. Lyons, Boston; George L. MacKinnon, Quincy; Jacob Mezer, Brighton; Eugene L. Richmond, Worcester; Lamar Souther, Boston; John S. Sprague, Boston; John C. Tate, Longmeadow; and Ralph Zupancic, Boston.

New Hampshire: Albert E. Barcomb, Rochester; Kenneth J. Daly, Manchester; and Kenneth L. Roper, Hanover.

Vermont: Louis W. Esposito, Rutland; and Bruce B. Rolf, St. Johnsbury.

MEDICAL INFORMATION OFFICE

Major General James C. Magee, retired, former surgeon general of the United States Army, has recently assumed his duties as executive officer of the information service of the Division of Medical Sciences, National Research Council. General Magee will devote full time to the organization of a central office in the National Research Council that will collect reports and records, dealing with military medical

practice, civilian practice as affected by the war, medical education and research and the distribution of diseases. This service has been made possible by a recent grant of \$75,000 by the Johnson and Johnson Research Foundation, of New Brunswick, New Jersey, to enable the National Research Council to assemble and disseminate medical information pertaining to the war effort. This enterprise is expected to fill a long-felt need in providing up-to-date information to the medical officers of the armed services, both in this country and abroad, and in making the experience of war medicine available, so far as possible, to civilian physicians.

NOTE

On the evening of December 30, ninety-six graduates of Tufts College Medical School were awarded their degrees and the majority were simultaneously commissioned in the Medical Corps of the Army or Navy. The honorary degree of Doctor of Science was conferred on two graduates of Tufts College Medical School: Brigadier General Raymond W. Bliss, of Washington, D. C., and Dr. Sara M. Jordan, of Boston.

CORRESPONDENCE

AN OPENING IN MONTAGUE

To the Editor:—The following letter from the Governor's office is self-explanatory. Perhaps some physician may wish to take advantage of this offer.

H. QUIMBY GALLUPE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

* * *

December 22, 1943

Dear Dr. Gallupe:

Mrs. George A. Cooke, of 813 Beacon Street, Boston (Kenmore 7956), is the widow of the only physician who was located in the town of Montague. She has made the offer of the use of the late doctor's office and equipment to any doctor who might be interested in setting up a practice in that town.

I pass this on for your information.

Sincerely yours,

[Signed] William A. McGivney
WILLIAM A. MCGIVNEY
Assistant Secretary to the Governor

State House
Boston

KÜMMELL'S DISEASE

To the Editor: In the November 18 issue of the *Journal*, appeared a medical eponym, "Kümmell's Disease," that was of special interest to me. While practicing in Hungary, I had two cases in my surgical ward—one in 1926 and one in 1928—both of which had the typical histories, symptoms and developments of Kümmell's disease, with negative tuberculin reactions and so forth. After learning from experience with the first case, I had made it a rule to immediately take x-ray films of all, even seemingly insignificant, injuries in the vertebral region. The films of the second patient, taken immediately after the accident, were entirely negative. The patient, a miner, resumed work about twelve days after the injury was incurred, but after an interval of many months developed typical gibbus formation with the usual x-ray findings. I sent the pictures and case histories to Dr. Kümmell and have on hand his reply, in his own handwriting, dated December 11, 1928. He wrote how happy he was to receive my information and that he considered it additional proof that Kümmell's disease—or as he later called it,

"post-traumatic vertebral disease"—actually existed. He also sent me the reports made by the director of the X-ray Laboratory of Hamburg University Medical School. The report on the pictures taken after the accident but without knowledge of the case history was "negative," and after the gibbus formation, "tuberculous spondylitis." After learning the history the diagnosis was changed to "typically so-called 'Kümmell's disease' or post-traumatic vertebral disease."

On Dr. Kümmell's urging, I had a paper published in 1928 about these two cases, with the x-ray pictures.

LOUIS A. SZIVES

309 Main Street
Great Barrington, Massachusetts

NOTICES

NEW ENGLAND ROENTGEN RAY SOCIETY

The next meeting of the New England Roentgen Ray Society will be held at the Harvard Club of Boston on Friday, January 21. There will be an x-ray conference from 4:30 to 6:00 p.m. on the topic "The Paranasal Sinuses." At 6:00 p.m., dinner will be served in Harvard Hall. At 8:00 p.m., the following program will be presented:

Radium in Present-Day Therapeutics. Dr. Douglas Quick.
Radiologic Problems in the Treatment of Carcinoma of the Skin (illustrated by slides). Dr. John T. Murphy.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 12, 1944, at 2:00 p.m.

Arrangements will be made, so far as possible, for candidates in military service to take the Part I examination (written paper and submission of case records) at their places of duty, the written examination to be proctored by the commanding officer (medical) or some responsible person designated by him. Material for the written examination will be sent to the proctor several weeks in advance of the examination date. Candidates for the Part I examination who are entering military service or who are now in service and may be assigned to foreign duty may submit their case records in advance of the above date by forwarding them to the office of the secretary. All other candidates should present their case records to the examiner at the time and place of taking the written examination.

The Office of the Surgeon-General of the United States Army has issued instructions that men in service who are eligible for Board examinations be encouraged to apply and that they request orders to detached duty for the purpose of taking these examinations whenever possible.

All candidates will be required to take both the Part I examination and the Part II examination (oral, clinical and pathological examination). Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held later in the year. Headquarters for the Part II examination will be the Hotel William Penn, Pittsburgh, Pennsylvania, from June 7 to 13, 1944. Notice of the exact time of the examinations will be sent to all candidates well in advance of the examination date. Candidates in service are requested to keep the secretary's office informed of any change in address. If a candidate in service finds it impossible to proceed with the examinations of the Board, deferment without time penalty will be granted under a waiver of the published regulations as they apply to civilian candidates.

Applications for the 1944 examinations are now closed. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

(Continued on page x)

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HOW TO IMPROVE THE TREATMENT OF FRACTURES*

CHARLES L. SCUDDER, M.D.†

BOSTON

IT IS appropriate to list this communication with war papers. There is no war work more important than that the medical profession should adjust itself to better results in the case of the injured. To accomplish this, and to have the hospital and the personnel of the hospital up to date when the war is over and the younger men return from the active war front, will be well worth while. It is to this end that I address you today, urging a real war effort.

Every member of the Society, no matter with what subject in medicine or surgery he is primarily concerned, should be familiar with first-aid care and transportation of the injured. The treatment of fractures, however, is very special work, and demands a doctor who has had a general surgical training. The art of surgery has been for years far in advance of all the sciences on which its future depended. Today, the sciences are overtaking the art and form the basis of sound treatment. Chronic duodenal and gastric ulcers were permitted to advance to perforation, peritonitis and fatal hemorrhage until comparatively recently. Injuries to the head, with or without fracture of the skull, invariably received a decompression operation, done by the surgeon first seeing the case. Today, one almost never hears of or sees a decompression operation because, with an increasing knowledge of the cerebrospinal fluid and its behavior following a blow on the head, especially with increasing signs, a diagnostic and sometimes a therapeutic lumbar puncture may be employed by the attending surgeon.

Fractures are now unwittingly allowed to go beyond the time at which successful treatment may be instituted. Such delay forever precludes the possibility of preventing disabling deformity. In some of these cases even death itself might be preferred to the permanent disability with which all are familiar.

The accident causing a fracture is instantaneous. The reparative processes begin immediately and

treatment should therefore begin without delay so that the reparative processes may be facilitated instead of hindered. By treating a fracture instantly, one treats the fracture alone; by treating it after delay, one treats the fracture together with its complications. Ordinarily, prompt treatment is easy; frequently, delayed treatment is difficult. Furthermore, delayed treatment is dangerous, and late treatment is lamentable.

During the course of years, fundamentals are bound to change. One cannot wish broken and displaced bones into position and cause them to unite by moral suasion, sending the patient on his way without a hitch. The methods available to the surgeon who deals with trauma are remarkable, and compel a modification of what once were regarded as fundamental principles. This is as it should be. We must not be bothered or alarmed by these tendencies; they all indicate improvement.

What can be done in Massachusetts to improve the results following the treatment of fractures? Some suggestions follow.

Proper first-aid care must be given to injured people. It is a fact of great importance that few practitioners of medicine and surgery in the United States are familiar with first aid. The war has stressed the value of first aid and has increased information about it among laymen. Physicians, in self-defense, are being obliged to learn something about it.

The injured should be immediately transported to a hospital. The American Red Cross textbook on first aid, which is used as the basis for instruction in first-aid care, is excellent. It contains more good methods of transportation than poor ones. It is not, however, perfect, and certain improvements will undoubtedly be made in subsequent editions. How should one transport to a hospital a man who has fallen from a tree and injured his back, or one with a probable broken neck? Can you answer these questions satisfactorily? You should be able to, because you may have to take care of someone who knows how these things ought to be done.

*Presented to the annual meeting of the Massachusetts Medical Society, Boston, May 25, 1943.

†Consulting surgeon, Massachusetts General Hospital.

An x-ray examination must be made to learn accurately the problem at hand. Adequate x-ray films should be taken to confirm and enlarge in detail the clinical diagnosis. I recently saw a switchman who had fallen from a boxcar and complained of pain in the back. Perfect x-ray films had been made, but for the sake of economy the films had been taken only from the second lumbar vertebra down to include the upper third of the femur. The patient was treated for seven weeks by rest in bed because there were no evidences of fracture in the parts x-rayed. After working for a month, he again complained of pain in the back. New x-ray films were taken, including the whole lumbar spine. A compression fracture of the first lumbar vertebra was seen and treated. This lesion was missed in the first instance because of inadequate x-ray films.

The doctor must evaluate his ability to treat the injury. Suppose that he is examining a child with a fracture of a long bone, having been called by the parents. Why was he called? The ordinary reason given is that he is regarded as the family doctor. He delivered the mother of this family of all her children. The mother says, "We have confidence in you." It is true that he has been caring for this family for years. But the notion that any doctor can treat a fracture is less prevalent than it used to be. This imaginary case raises the question of the competency of a doctor to treat a fracture. There should arise in his mind the questions, "Am I prepared to treat this fracture? Do I know how to find out exactly what the damage is? Am I competent to decide what is to be done in this particular case, and to do it?" The doctor may say to himself, "I need the money. I can take care of this fracture. The family thinks I am able, and that is a great asset. I will make a bluff at it, and if I get stuck, I shall call for help." Under the economic conditions of today, it may be difficult for a doctor to give up such a case.

If the physician is unable to give proper treatment, he must call a good consultant as soon as possible. By securing advice early, he may prevent a Volkmann's contracture. To cite an example, in a town not far from Boston, I held a fracture clinic. Cases were brought to the clinic from outlying districts. Seven children came in, each with an established Volkmann's contracture following a supracondylar fracture of the humerus. No splints or bandages had been used. These cases point a moral and dramatically accentuate the importance of properly treating injuries in the region of the elbow joint. Each of these bad results might have been avoided. Unwarranted responsibility is a risk to the patient and to the reputation of the doctor. If the attending physician asks for an early consultation, he gives both his patient and the consultant a better chance. He rises in the esteem of his patient and in the good will of the community in which he practices.

Associated injuries must be recognized. The fracture of the bone in any case may be the least important of the injuries received. There may be injuries to the brain, spinal cord, or lung, with an associated pneumothorax or a hemopneumothorax; injuries to the abdominal viscera, with hemorrhage into the abdominal cavity, and possibly with rupture of the viscera; or injury to the urinary bladder, associated with fractures of the pelvis.

One does not have to qualify as a neurosurgeon, a thoracic surgeon, a genitourinary surgeon, an abdominal surgeon, an orthopedic surgeon or a vascular surgeon, but anyone treating a fracture should be familiar with the fundamentals of these special branches of surgery so that he may know when there is need for consultation with a specialist.

In treatment, the doctor must use a method with which he is perfectly familiar. If a surgeon has been securing good functional results by the use of certain methods, he should by all means continue to use them. Nevertheless, I wonder how many of you are familiar with your results in the treatment of fractures.

One should be conversant with known operative procedures and results. There are fractures that should be treated initially by operative methods when the local equipment is available and intelligently used.

One should be familiar with nonoperative treatment. Nonoperative methods may require great skill. Their results are often brilliant.

More pull and less manipulation should be employed in treating any fracture. Far greater initial traction should be used, for sufficient traction may bring about reduction of the fracture. Instead of using 5 or 10 pounds of traction at the beginning of treatment, and gradually increasing it, ordinarily one should begin with 25 or 30 pounds.

The period of aftercare or convalescence is a time of great importance. This should be regarded as a time of active treatment. One reason for Dr. Otto Hermann's successful treatment of fractures of the os calcis at the Boston City Hospital is dependent in great measure on his supervision of the minute details of the aftercare of these cases. In the convalescing period one may profitably spend a little time instructing the patient in muscle re-education, weight bearing, correct shoes, exercises and the use of crutches, and may thus gain the patient's confidence and directly influence the result of treatment.

In the United States and in the provinces of Canada, the American College of Surgeons has already established ninety regional fracture committees, with the object of improving fracture treatment in these communities. Obviously, certain states have more than one committee. Texas, Pennsylvania, New York, Indiana, and California are splendidly organized, and are accomplishing much. Massachusetts has a regional committee, with sixteen subcommittees, in Lowell, Beverly,

Quincy, Northampton, Gardner, Melrose, Haverhill, Cotuit, Brockton, Greenfield, Taunton, Worcester, Newburyport, New Bedford, Springfield and Pittsfield, which carry on their work through the local hospitals. During the past week, I received a report on the activities of the Flint (Michigan) regional committee, which reads as follows:

We have had fracture conferences of my staff each Friday, from 4.30 to 6.30 p.m. All fracture problems of the previous week are discussed at these meetings, and they represent 85 per cent of the cases of fracture admitted to the Hurley Hospital. Similar meetings are held at selected intervals for the Fracture Service of St. Joseph's Hospital in this city. All fracture cases are assigned to members of the fracture services, and these are presented, both formally and informally, as the need arises.

All the ambulance drivers have received adequate first-aid instruction through various agencies, and each ambulance is equipped with splints, which, with few exceptions, are properly used. Patients are being brought to the hospitals with some type of splinting apparatus, usually a Thomas splint for the lower extremity, and a Murray-Jones splint for the upper extremity.

Fracture cases of all kinds at Hurley Hospital from July, 1941, to July, 1942, numbered 1085. About eighty per cent were handled by my staff and myself, either as staff or private cases, and the remainder were cared for by surgeons handling the occasional fracture. The latter situation is unavoidable inasmuch as Hurley Hospital is an open hospital. However, we are able to control the minor percentage by example, and through the co-operation of the X-ray Division. These patients are, in our opinion, handled according to the prevailing standards that we have been able to establish by this persistent method of fracture education in this community over the past twelve years.

We keep a book in which every fracture admitted to the hospital is tabulated. We also keep a conference book, in which important comments during reviews of the x-ray films are noted. Furthermore, pertinent recent information regarding this division of surgery is posted on a bulletin board in the emergency room for the Department of Traumatic Surgery. We manage to keep one live research problem under way each year.

We have nine members on the regional fracture committee.

I believe that your personal co-operation with the several regional fracture subcommittees in Massachusetts along the lines suggested in this report from Flint, Michigan will help very much in improving the results of fracture treatment. Find out who is the chairman of the subcommittee nearest your town. If you are a consultant at the local hospital and if you are on active duty there, try to initiate a follow-up of the cases of fracture, and analyze these results at some regular staff meeting, showing the x-ray films. It makes no difference how few cases of fracture are treated at your hospital. These cases should be carefully studied by the whole staff. Invite doctors to the hospital meetings so that all in your community may profit by a review of the cases. Consider seriously the ten or twelve suggestions I have made as guides. There is no reason why Massachusetts should not stand abreast of the advances taking place in fracture treatment at this time. Each one of us can help.

374 Commonwealth Avenue

DIVERTICULITIS OF THE COLON*

A Review of the Literature and an Analysis of Ninety-One Cases

EDWARD L. YOUNG, M.D.,† AND EDWARD L. YOUNG, III, M.D.

BOSTON

DIVERTICULUMS of the large bowel were noted by Friend as early as 1730, but a disease entity was not ascribed to them until Cruveilhier's work in 1849. Ten years later the first report of a complication of rupture—a sigmoidovesical fistula—was made by Jones, but little attention was paid to the condition until W. J. Mayo¹ in 1907 described resection of the sigmoid in 5 cases of chronic obstructive diverticulitis. The value of the roentgen ray as an aid in diagnosis was not fully appreciated in this country until 1915.² Since then there has been a gradual evolution in the technic of handling these cases—from radicalism to conservatism. The disease is of relatively common occurrence, errors in diagnosis are not infrequent, and both the morbidity and mortality are altogether too high.

INCIDENCE, AGE AND SEX

The incidence of diverticulosis of the colon—a prerequisite of diverticulitis—has been estimated

at 3 to 10 per cent. A compilation of statistics³⁻⁸ shows an incidence of 5.2 per cent in 70,572 colons examined by barium and autopsy. It is difficult to obtain significant figures on the percentage of cases of diverticulosis progressing to diverticulitis. It is usually stated that from 12 to 15 per cent do so, but in three series totaling 3915 cases with diverticulosis of the colon the incidence of diverticulitis was 34.3 per cent.^{6, 7}

Of patients with diverticulitis about 22 per cent are operated on.⁹⁻¹² Because, however, of the trend in treatment away from surgery and the significant number of patients operated on with erroneous diagnoses, the actual percentage of cases of diverticulitis reaching the operating table is probably lower than this. Arnheim¹³ collected from the literature 3399 cases of diverticulitis and found complications that might have necessitated surgery in 15 per cent—perforation with abscess formation or general peritonitis, peridiverticulitis with formation of a tumorlike mass, and sigmoidovesical fistula.

Diverticulitis is primarily a disease of adult life. Brown¹⁰ has estimated that only 0.3 per cent of all

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An x-ray examination must be made to learn accurately the problem at hand. Adequate x-ray films should be taken to confirm and enlarge in detail the clinical diagnosis. I recently saw a switchman who had fallen from a boxcar and complained of pain in the back. Perfect x-ray films had been made, but for the sake of economy the films had been taken only from the second lumbar vertebra down to include the upper third of the femur. The patient was treated for seven weeks by rest in bed because there were no evidences of fracture in the parts x-rayed. After working for a month, he again complained of pain in the back. New x-ray films were taken, including the whole lumbar spine. A compression fracture of the first lumbar vertebra was seen and treated. This lesion was missed in the first instance because of inadequate x-ray films.

The doctor must evaluate his ability to treat the injury. Suppose that he is examining a child with a fracture of a long bone, having been called by the parents. Why was he called? The ordinary reason given is that he is regarded as the family doctor. He delivered the mother of this family of all her children. The mother says, "We have confidence in you." It is true that he has been caring for this family for years. But the notion that any doctor can treat a fracture is less prevalent than it used to be. This imaginary case raises the question of the competency of a doctor to treat a fracture. There should arise in his mind the questions, "Am I prepared to treat this fracture? Do I know how to find out exactly what the damage is? Am I competent to decide what is to be done in this particular case, and to do it?" The doctor may say to himself, "I need the money. I can take care of this fracture. The family thinks I am able, and that is a great asset. I will make a bluff at it, and if I get stuck, I shall call for help." Under the economic conditions of today, it may be difficult for a doctor to give up such a case.

If the physician is unable to give proper treatment, he must call a good consultant as soon as possible. By securing advice early, he may prevent a Volkmann's contracture. To cite an example, in a town not far from Boston, I held a fracture clinic. Cases were brought to the clinic from outlying districts. Seven children came in, each with an established Volkmann's contracture following a supracondylar fracture of the humerus. No splints or bandages had been used. These cases point a moral and dramatically accentuate the importance of properly treating injuries in the region of the elbow joint. Each of these bad results might have been avoided. Unwarranted responsibility is a risk to the patient and to the reputation of the doctor. If the attending physician asks for an early consultation, he gives both his patient and the consultant a better chance. He rises in the esteem of his patient and in the good will of the community in which he practices.

Associated injuries must be recognized. The fracture of the bone in any case may be the least important of the injuries received. There may be injuries to the brain, spinal cord, or lung, with an associated pneumothorax or a hemopneumothorax; injuries to the abdominal viscera, with hemorrhage into the abdominal cavity, and possibly with rupture of the viscera; or injury to the urinary bladder, associated with fractures of the pelvis.

One does not have to qualify as a neurosurgeon, a thoracic surgeon, a genitourinary surgeon, an abdominal surgeon, an orthopedic surgeon or a vascular surgeon, but anyone treating a fracture should be familiar with the fundamentals of these special branches of surgery so that he may know when there is need for consultation with a specialist.

In treatment, the doctor must use a method with which he is perfectly familiar. If a surgeon has been securing good functional results by the use of certain methods, he should by all means continue to use them. Nevertheless, I wonder how many of you are familiar with your results in the treatment of fractures.

One should be conversant with known operative procedures and results. There are fractures that should be treated initially by operative methods when the local equipment is available and intelligently used.

One should be familiar with nonoperative treatment. Nonoperative methods may require great skill. Their results are often brilliant.

More pull and less manipulation should be employed in treating any fracture. Far greater initial traction should be used, for sufficient traction may bring about reduction of the fracture. Instead of using 5 or 10 pounds of traction at the beginning of treatment, and gradually increasing it, ordinarily one should begin with 25 or 30 pounds.

The period of aftercare or convalescence is a time of great importance. This should be regarded as a time of active treatment. One reason for Dr. Otto Hermann's successful treatment of fractures of the os calcis at the Boston City Hospital is dependent in great measure on his supervision of the minute details of the aftercare of these cases. In the convalescing period one may profitably spend a little time instructing the patient in muscle re-education, weight bearing, correct shoes, exercises and the use of crutches, and may thus gain the patient's confidence and directly influence the result of treatment.

In the United States and in the provinces of Canada, the American College of Surgeons has already established ninety regional fracture committees, with the object of improving fracture treatment in these communities. Obviously, certain states have more than one committee. Texas, Pennsylvania, New York, Indiana, and California are splendidly organized, and are accomplishing much. Massachusetts has a regional committee, with sixteen subcommittees, in Lowell, Beverly,

enema are used in arriving at a diagnosis. A negative examination by either method does not, however, exclude a diagnosis of diverticulitis. Only rarely can diverticular openings be seen with the sigmoidoscope, but there are definite changes in the bowel suggestive of the diagnosis — spasm, hypermotility with varying degrees of obstruction, immobility, sharp angulation, mucosal edema and signs of an extraluminal mass. Jackman and Pumphrey²³ made a correct diagnosis of diverticulitis in 66 per cent of a series of cases from sigmoidoscopy alone. Diverticulums were seen, however, in only 14.5 per cent. Brown and Marcle¹¹ found that suggestive evidence could be discovered by sigmoidoscopy in only 24 per cent of 218 cases, and diverticular openings in only 9 per cent.

The barium enema is the most accurate diagnostic procedure. Figures on the percentage of accuracy are practically nonexistent. In a series of 30 cases reviewed by Graham,¹⁶ diagnosis by x-ray was correct in only 57 per cent, indeterminate in 17 per cent, and wrong in 26 per cent. Of the cases that were wrongly diagnosed, 4 were called diverticulitis; 3 of these were later proved to be cancer, and 1 proved to be normal. Three were diagnosed as cancer and later proved to be diverticulitis; and 1 was diagnosed as normal and later proved to be diverticulitis. Morrison²⁴ believes, however, that well over 90 per cent of diverticulums can be seen. The differentiation of diverticulosis and diverticulitis cannot always be made at examination, but this seems to be largely due to the fact that patients are not studied by barium enema during the clinically inflammatory stage. In obstructive cases the differentiation of carcinoma and diverticulitis is often extremely difficult.²⁵⁻²⁷ X-ray films show uncomplicated diverticulums as rounded out-pocketings filled with barium in relief along the border of the bowel wall.

Diverticulitis is manifested by spasm, by hypermotility with varying degrees of obstruction due to fibroblastic reaction or by spasm. Tenderness may or may not be present.

TREATMENT

As with any disease, the best treatment is prophylaxis. Following a diagnosis of diverticulosis, measures should be instituted to avoid the factors known to predispose to diverticulitis, such as overdistention of the bowel, hard, coarse fecal material, degenerative changes and obesity. A low-roughage diet and sufficient mineral oil or other bland laxative to promote regular, soft-formed movements eliminate the usual mechanical factors. Tincture of belladonna to relieve spasm is always beneficial. All irritative cathartics are contraindicated, especially strong saline solutions since their prolonged use leads to hypertonicity of the rectal sphincter. All efforts should be aimed at cultivation of regular bowel habits.

With the onset of diverticulitis, further steps are indicated — a temporary soft diet to rest the inflamed sigmoid, bed rest, local heat and antispasmodics. There are several methods of applying heat locally — hot stupes to the abdomen, the Elliott method and warm colonic irrigations. Roberts²⁸ and Friedenwald²⁹ mention the use of large barium enemas in both subsiding and acute diverticulitis. One of us (E. L. Y.) has used repeated small instillations of dilute barium with excellent results. The method is as follows in acute cases: 30 gm. of x-ray barium in 90 cc. of warm water is instilled rectally twice a week, following a cleansing enema, until subsidence; then once a week as long as the forbearance of the patient lasts. Kimpton³⁰ uses barium by mouth with the same timing. The barium fills the diverticulum, shutting out irritating feces, and is itself mildly soothing.

As noted above, about 22 per cent of cases come to surgery, but indications for surgical intervention are still unsettled and the trend in therapy is toward conservatism. There seem to be five general indications for surgery: acute perforation with spreading peritonitis, sigmoidal obstruction, formation of a fistula, a localized abscess and inability to differentiate diverticulitis and cancer. Technical details covering the choice of the time to operate and the procedure to be adopted are too varied to warrant discussion here; the reader is referred to the excellent review by Laufman.³¹ Graham¹⁶ has emphasized the two cardinal principles: restoration of chemical balance while using the expectant measures of bed rest, local heat, sedatives and proper control of intake, and the simplest operative procedure. The importance of the latter principle is amply proved by figures collected by Laufman. In a series of 434 patients, there was an operative mortality of 11.8 per cent following conservative procedures, — colostomy alone, colostomy and subsequent closure, cecostomy, drainage of abscess, exploratory laparotomy, separation of adhesions, excision of inflamed diverticulums and repair of colovesical fistulas without resection, — as against a mortality of 21 per cent following radical procedures — resection after colostomy, Mikulicz resection, resection and anastomosis after colostomy, obstructive resection with subsequent closure of colostomy and one-stage resection.

Results. It is impossible to estimate the prophylactic value of measures undertaken when diverticulosis alone is present. Brown and Marcle¹¹ made a follow-up study of 192 patients with diverticulosis who had followed a careful medical regime. Of these, 145 had had no symptoms suggestive of diverticulitis, 46 had died of unrelated or unknown causes, and 1 had died of "questionably" related causes. They likewise reviewed 238 cases of diverticulitis treated on a medical regime. Of these patients, 118 (50 per cent) were "cured," 23 per cent were not affected, and 4 per cent died of related causes.

From a review of the literature, Laufman³¹ has concluded that of any large series of cases 18 per cent receive no benefit from any form of therapy and the mortality is 16 per cent. The latter figure coincides with the latest one (14 per cent) reported by Lockhart-Mummery.³²

* * *

The following sections and Table 1 are based on a series of 84 cases of diverticulitis of the sigmoid seen at the Faulkner Hospital from 1933 to 1942, inclusive. For analytical purposes the cases have

TABLE 1. *Signs, Symptoms and Findings in Chronic and Acute Diverticulitis*

SIGN, SYMPTOM OR FINDING	CHRONIC DIVERTICULITIS	ACUTE DIVERTICULITIS
	%	%
Change in bowel habits	79	46
Rectal bleeding	33	20
General digestive complaints	53	41
Pain	63	95
Tenderness	63	93
Elevated temperature	12	80
Elevated white-cell count	19	80
Positive sigmoidoscopic findings	71	—
X-ray diagnosis (barium enema):		
Diverticulosis	98	88
Diverticulitis	78	84

been divided into chronic and acute, as determined principally by the presenting complaint, immediate history, physical examination and white-cell count, and partly by the known duration of the colonic disease.

INCIDENCE

During 1941 and 1942, barium enemas were given to aid in the diagnosis of abdominal symptoms in 423 cases, and diverticulosis of the colon was demonstrated in 154 (36 per cent). In 89 (58 per cent) of these, diverticulitis was shown by x-ray examination. Both the percentage of diverticulums found and the number of these patients having diverticulitis are much higher than those found in the literature. The suggested explanation—namely, that this disease is much more frequent than is generally supposed—gives it a more prominent place than it usually receives.

CHRONIC DIVERTICULITIS

The distinction between mild, chronic diverticulitis and diverticulosis is often a debatable one. In the 43 patients with chronic diverticulitis have been included those with a clinical and x-ray diagnosis of diverticulitis and a history consistent with diverticulitis, together with x-ray evidence of a diverticulum, with or without attendant irritability and tenderness or spasm of the colon.

Age and sex. The ages ranged from thirty-seven to eighty-one years, with 88 per cent of the cases divided equally between the fifth, sixth and seventh decades. Twenty-four (56 per cent) of the patients were women.

History. A change in bowel habits was the outstanding complaint in 34 patients (79 per cent).

There was constipation in 14 cases, diarrhea in 7 cases, and both in 6 cases. Gross bleeding was present in 9 cases, and occult blood in 5. Excluding 1 case of gross bleeding from carcinoma, the incidence of rectal bleeding due to diverticulitis was 33 per cent. Of the 9 patients without changes in bowel habits, 2 complained of indigestion, 2 of lower abdominal pain, 1 of pain in the left lower quadrant, 1 of pain in the right back, and 3 of general debility, loss of strength and anorexia. The patients with indigestion had associated diaphragmatic hernias, and one with low abdominal pain had ascites on a cirrhotic basis. One patient had relief of low abdominal pain from defecation.

The next most frequent complaints were abdominal pain (27 cases, or 63 per cent) and general digestive disturbances, such as gas, indigestion, nausea and vomiting (23 cases, or 53 per cent). There were other scattered symptoms such as loss of weight (5 cases), loss of strength and appetite (6 cases) and urgency and nocturia (2 cases).

Physical examination. Abnormal physical findings were minimal. Sixteen patients (37 per cent) had negative examinations (excluding other disease). Twenty-seven had abdominal tenderness, usually mild but occasionally marked and with spasm. This was below the umbilicus in 18 cases, in the left lower quadrant in 13, in the right lower quadrant in 3, throughout the lower abdomen in 2, in the left upper quadrant in 4, on the right side in 2, and diffuse in 1; the pain was not localized in 2 cases. A mass was made out rectally in 3 cases, in one of which it proved to be carcinoma, vaginally in 1, and in the left lower quadrant in 2. Distention was noted in 4 cases.

Temperature and white-cell count. These corresponded to the mildness of the symptoms and signs. Thirty-eight patients (88 per cent) had normal temperatures; in the remainder the temperature never went above 100°F. and rapidly fell to normal. The white-cell count was normal (below 10,000) in 35 cases (81 per cent) and below 13,500 in the remainder.

Sigmoidoscopy and barium enema. Sigmoidoscopy was done in 7 cases. No diverticulums were seen, but there was evidence suggestive of the diagnosis in 5 of these (71 per cent)—spasm of the lower sigmoid and rectum in 4 and a mass in 1.

Barium-enema studies were done in 41 cases and a roentgenologic diagnosis of diverticulitis of the colon was made in 32 (78 per cent). Diverticulums were seen in another 8 cases (20 per cent). Diverticulums were seen in the descending colon in 19 cases, in the transverse colon in 13 and in the ascending colon in 8. There were four partially correct or totally erroneous diagnoses. Two cases diagnosed as carcinoma of the sigmoid proved at operation to be diverticulitis; 1, diagnosed as diverticulitis, proved at autopsy to be diverticulitis and carcinoma of the rectum; 1, diagnosed as diverticulitis, proved at autopsy to be diverticulitis and carcinoma of the

rectum; 1, diagnosed as obstruction of the lower sigmoid was operated on for carcinoma and proved to be diverticulitis; and 1, diagnosed as abscess cavity, proved at operation to be due to diverticulitis. Thus, x-ray studies with a barium enema in the chronic group may be said to be 98 per cent correct in determining the presence of diverticula of the colon. The actual diagnosis of diverticulitis is, in the mild cases at least, of little significance for two reasons: the enema may be given after subsidence of the acute stage, and the clinical picture as seen by the physician during the acute stage supported by x-ray evidence of a diverticulum should be sufficient for a diagnosis.

Treatment. Seven operations were performed (excluding a case with known diverticulitis of the sigmoid but with a carcinoma of the rectum in addition), making an operative incidence of 16 per cent. Two patients were explored because of inability to make a differential diagnosis between diverticulitis and carcinoma, and one of these had resection preceded by transverse colostomy. Three were operated on with a diagnosis of carcinoma of the sigmoid with resection in one, a two-stage Mikulicz resection in another, and drainage of an abscess in the third. One patient was operated on for lysis of adhesions diagnosed preoperatively as diverticulitis, 1 for evacuation of an abscess obstructing a previous suture line (from resection for carcinoma of the splenic flexure) that proved to be due to a ruptured diverticulum. One patient died of massive pulmonary collapse, a mortality of 14 per cent.

The procedures used for the 4 erroneously diagnosed cases were colostomy followed by resection, a two-stage Mikulicz resection and drainage of abscess (two cases).

The hospital stay averaged eight days for the nonoperative cases and twenty-seven days for the operative ones—excluding the case of resection of the splenic flexure.

ACUTE DIVERTICULITIS

In the 41 cases of acute diverticulitis, as compared with the chronic cases, there was intensification of symptoms and signs, more operations were done, and the mortality was higher.

Age and sex. The age distribution was a decade younger than in the previous groups, 85 per cent of the cases occurring between forty and sixty-nine. There was a slight preponderance of males (51 per cent).

History. Pain was the chief complaint in 39 cases (95 per cent), in 24 of which it was below the umbilicus. It was in the left lower quadrant in 16 cases and hypogastric in 8, in 3 of which it was most marked in the right lower quadrant. There were several striking examples of the fallibility of localization of pain as indicating the site of disease. One patient had midepigastria pain, 1 in the right upper quadrant, 1 in the left testicle and 1 in the vagina.

Only 19 patients (40 per cent) had a change in bowel habits, and 16 of these stated that the change was directly associated with the present entry. There was obstipation of one to several days' duration in 6 cases, an urge to defecate without results in 3, and relief of pain on defecation in 3. Gross bleeding was present in 4 cases, and occult blood in 4, making an incidence of bleeding of 20 per cent.

There were digestive complaints in only 17 cases (41 per cent), with vomiting in 11, nausea with or without vomiting in 8 and anorexia in 3.

Urinary symptoms became more prominent in this group, occurring in 8 cases (20 per cent). Four of these patients had burning or sharp pain on urination; 1 patient had urgency and frequency. Other symptoms were pressure and pain around the bladder and vagina.

Physical examination. Thirty-eight patients (93 per cent) had abdominal or pelvic tenderness, in 31 below the umbilicus; the tenderness was greatest in the left lower quadrant in 21 and in the right lower quadrant in 6. One had tenderness in the right upper quadrant, and 5 on rectal or vaginal examination. Distention was present in 18 (44 per cent). A mass was felt in 16 cases (39 per cent)—in the left lower quadrant on abdominal examination in 10, and on rectal or vaginal examination only in 6.

Temperature and white-cell count. The temperature was elevated in 33 cases (80 per cent), rising to 100°F. or less in 14, to 101°F. in 11, and to 102°F. in 4. In 1 case it reached 103.8°F. The white-cell count was likewise elevated in 33 cases, reaching 12,000 in 7, 15,000 in 10, 20,000 in 10, 30,000 in 3, and 33,000 in 1.

Barium enema. No sigmoidoscopic examinations were done. A barium enema examination was done in 25 cases (61 per cent). In 21 of these, the diagnosis was diverticulitis and 1 diverticulosis in a spastic sigmoid; in the other 3 it was spastic bowel, complete obstruction at the junction of the descending colon and sigmoid and an obstructive lesion at the midsigmoid, respectively. The last case was diagnosed as diverticulitis by barium enema four days later, the first two at operation. Obstruction was present in 5 cases—complete in 3 and partial in 2. Barium was seen outside the bowel in 2 cases, and in both there was complete recovery without operation then or later.

Treatment. Proctoscopy was done in 1 case and a mass pressing on the lumen of the lower bowel was noted. Surgical procedures were carried out on 21 patients (51 per cent), with errors in diagnosis in 6 cases and a mortality of 19 per cent. The erroneous diagnoses were acute appendicitis, twisted ovarian cyst (3 cases), ectopic pregnancy and carcinoma of the sigmoid. The last case was operated on primarily for fibroids. A mass in the sigmoid was found and was believed to be carcinoma. Colostomy was done, and at a second operation resection was performed; no carcinoma was found. Simple drain-

age was carried out in 9 cases, colostomy in 2, a one-stage resection in 1, and a Mikulicz resection in 2. Three patients died within ten days of operation, of embolus; 1 died seven years later as a result of a chronic draining pelvic abscess.

SUMMARY AND CONCLUSIONS

A brief review of the literature on diverticulitis of the colon is given, and the symptoms, signs and treatment of 84 cases at the Faulkner Hospital are presented.

Certain facts stand out as important: blood in the stool was found in 26 per cent of the cases where no cause other than the diverticulitis was found; the incidence of this condition was much higher in this series than in others, which suggests that in a true cross section of disease as seen by the general practitioner the condition should be oftener recognized and treated; conservative treatment, especially the use of x-ray barium either by mouth or where possible by rectum, gives a high percentage of relief; and when surgery is needed the simplest procedure possible gives the lowest mortality.

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TRANSIENT NERVOUS HYPERTENSION AS A MILITARY RISK*

Its Relation to Essential Hypertension

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A COMMON problem is that of male adults between the ages of twenty-one and forty-five, usually in the twenties, well qualified personally and physically for service in the armed forces except for transient elevations of the blood pressure. The systolic pressure varies from 140 to 160 mm., and occasionally higher, and the diastolic pressure ranges from 95 to 110, and rarely as high as 120. About one third of the subjects have only systolic hypertension. Occasionally nervous hypertension has previously been noted by the family physician or an insurance examiner or at a routine school or college examination. As a rule this hypertension was transient. Frequently the subject is activated and energetic, perspires freely, and has a slight to moderate tachycardia and a slight tremor. He resembles slightly a patient with hyperthyroidism. He is anxious to serve and is afraid his blood pressure will keep him out. In the more marked cases, the applicant is positively conditioned to the determination of his blood pressure. The presence of the examiner or even the sight of the sphygmomanometer causes a feeling of tenseness, sweating, tachycardia, sometimes hyperpnea, erection of the hairs and also a rise in blood pressure. In short, one observes a total sympathetic adrenergic response. With rest and reassurance the blood pressure descends, and one obtains readings within normal limits early and late in the day for three successive days.

During one month at the Office of Naval Officer Procurement, Boston, 222 (14 per cent) of 1574 applicants had mild variable hypertension at the initial examination. This is the expected incidence. One of us (R. S. P.) found early variable hypertension in 10 per cent of 3598 college men. Two other unpublished observations on smaller series showed 11 per cent in a mixed group of normally employed white-collar workers aged twenty to seventy, and 12 per cent among male graduate students.

Applicants with nervous hypertension are men aged from eighteen to fifty, the majority being in their twenties or thirties. Organic changes as

judged by the history, physical examination and urine examination are absent. The blood pressure itself is transiently elevated rather than transiently normal, as in early, true essential hypertension. Slightly over half the subjects have a family history of degenerative vascular disease in one or at the most two parents, grandparents or siblings. A random sampling of 26 applicants with nervous hypertension showed that 14 had both systolic and diastolic hypertension, 10 had a systolic hypertension only, and 2 had diastolic hypertension only. In 12 of the cases with systolic and diastolic hypertension the blood pressure fell, with an average drop of 19 systolic, 14 diastolic, to normal on the second or third day, and in 7 of the 10 with systolic hypertension it fell, with an average drop of 14, to normal. In 1 of the 2 cases with diastolic hypertension the blood pressure returned to normal. Its response to exercise and to change of position was not significantly different from that of normal controls.

Of cold tests² on 27 of this group, in 6 there was a fall of either systolic or diastolic pressure or both. In the others the average rise in diastolic pressure was 12, only 4 men showing a rise of 20 or more. A control series of tests on 18 miscellaneous hospitalized patients without cardiovascular disease showed an average systolic rise of 11, with a fall of 5 in one, and an average diastolic rise of 15. Only 3 showed a systolic rise of 20 mm. or more, and only 4 a diastolic rise of the same degree. On the other hand, cold tests on 30 patients with definite though mild, benign essential hypertension with minimal organic changes all showed definite pressor responses, the average systolic rise being 26, and the pressure response was 20 or more in 20 patients. The average diastolic rise was 18. It is evident that definite essential hypertension, although mild, is associated with greater and more persistent pressor responses to cold than is nervous hypertension in a random sampling of applicants. However, a rise of the blood pressure above accepted limits, even when transient, at the very least indicates that the subject has a greater chance of showing hypertension at later physical examinations.^{1, 2, 4} Hyper-reactors to mental stress incident to military physical examinations, like hyper-reactors to the cold test,² may be considered to be potentially hypertensive. Statistical studies suggest that even when blood pressures are within generally accepted normal limits, persons with pressures at the lower limits of normal are less likely to develop subsequent hypertension than are those with pressures at the upper

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EQUINE ENCEPHALITIS

Many of the epizootiologic and epidemiologic characteristics of equine encephalitis have been clarified by the great amount of research accomplished in this disease in the last ten years. It is still uncertain, however, whether horses, wild and domestic fowls or other animals serve as the principal reservoir for human infection. It is quite possible that the horse is merely a chance victim, like the human being, and plays little part as a reservoir of the virus. Circumstantial support of this view is given when one considers the fact that in the last few years the incidence of equine encephalitis in horses has dropped considerably, whereas, largely because of better diagnostic facilities and reporting, recognized cases in human beings have increased.⁷ It is difficult to conjecture a comparison of equine and human infection prior to the use of adequate diagnostic methods.

The declining incidence of the disease in horses within the last few years has been developing a false sense of security in the minds of many horse owners. The reasons for this decline are difficult to evaluate when one considers the recent widespread use of equine vaccination, as well as possible biologic variables, such as decreased pathogenicity of the virus and fewer reservoirs or vectors. A somewhat analogous situation exists in human beings with such diseases as smallpox, diphtheria, measles and scarlet fever.

It is sound preventive medicine to reduce to a minimum, whenever feasible, the probable reservoirs of infection. In view of the still incomplete knowledge concerning the inter-relation of equine and human infection, it would be unwise to relax the effective preventive measure, intradermal chick-embryo vaccine, as applied to horses. An unvaccinated, highly susceptible horse population may well cause serious consequences in human beings. An official recommendation by the health officer to recalcitrant horse owners in his district to have horses vaccinated properly by a veterinarian would, therefore, be well within the province of his duty to the community.

RABIES

Few diseases can cause such public clamor for action as can an outbreak of rabies. Regulations concerning rabies control, too often unenforced, differ widely in various communities. A workable plan that will satisfy the public demand as well as the requirements of prevention is highly desirable.

Webster⁸ states in his excellent book on rabies, "His [the veterinarian's] skill and efforts in recognizing early rabies constitute a potent first line of attack in the control program." The advantages of facilities for the isolation and clinical observation of suspected rabid dogs, afforded by the veterinarian to the health officer, can be well appreciated.

Furthermore, in another highly important phase of the rabies-control program—the vaccination of dogs—the veterinarian and health officer can work together.

Until last year, the efficacy of prophylactic rabies inoculations in dogs with biologic products that had been on the market was rightly questioned. The biologically statistically significant experiments of Leach and Johnson,^{9, 10} however, speak well for the effectiveness of a practical single-inoculation procedure. The work of Webster and Casals¹¹ shows great promise of yielding an even more effective marketable vaccine. Health officers, therefore, who were formerly hesitant about advising annual vaccination can now recommend a vaccine of proved potency as part of their control program.

Many progressive health departments advise the annual vaccination of dogs on a voluntary basis. Veterinarians are employed for a few days each year, and the cost to the dog owner is nothing, or merely that of the vaccine. Unless the project is well advertised, the co-operation on the part of the owner is usually fairly poor. For a really effective preventive program the following procedures should be enforced: elimination of stray dogs, proper restraint of dogs when outside the house, licensing of all dogs and compulsory annual vaccination. The first has become more difficult to practice because of the lack of personnel. The second is hard to enforce except in rabies scares. A combination of the last two can do much to offset the effect of the first two because of the intimate association with the dog that, when the dog's statement be required, certifying that the dog is vaccinated with an approved vaccine, vaccination can be enforced by a veterinarian employee.

There are several diseases that are often countered by veterinarians, of which the health officer should be aware.

Leptospirosis. This is a disease that is being increasingly recognized by veterinarians. *Leptospira canicola*, which is much more common than is *L. icterohaemolyticus*.

Ornithosis. The discovery of this disease in yard fowl¹² may indicate another source of infection for the health officer. At present, the diagnosis of ornithosis by the local veterinarian with the means at his disposal is difficult. Possibly future investigations will overcome this obstacle.

Listerellosis. The natural mode of transmission of this disease, which sporadically attacks cattle, sheep, goats, chickens and human beings, is still unknown.

Tick infestation of dogs. As is well known, the wood tick and American dog tick commonly infest dogs.

festing dogs in this country are carriers of the rickettsial organism that causes Rocky Mountain spotted fever. The questioning dog owner may be referred to the veterinarian to help solve the problem of deticking his dog.

Food Sanitation. A recommendation by health officers for the inclusion of veterinarians on local boards of health should prove advantageous. The veterinarian's knowledge of food sanitation—as evidenced by the work of the Veterinary Corps of the United States Army—and disease control would be valuable in the effective performance of a board's duties.

SUMMARY

Various ways in which the veterinarian can be of assistance to the health officer are discussed, and increased utilization of the former by the latter is recommended.

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Erratum. In the paper "The Grave Infections of the Hand" by Major Flynn, which appeared in the December 9 issue of the *Journal*, the abbreviation "gr." should be changed to "gm." in two places: page 899, column 1, the third and fourth lines from the bottom.

MEDICAL PROGRESS

TUBERCULOSIS

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TUBERCULOSIS is a disease of many different phases and, unless arbitrary boundaries are established in advance, discussion of the subject could continue endlessly. This year, even more than in the past, emphasis falls on the war and its relation to tuberculosis. Commenting with some skepticism on the predicted decline in tuberculosis mortality, King,¹ nine months before Pearl Harbor, pointed out that "war may upset all calculations." Fortunately, the death rate from tuberculosis in the United States has continued to fall,^{2,3} but wartime experience in other countries^{2,4,5} compels one to temper optimism with caution.

TUBERCULOSIS AND THE WAR

The impact of the war on tuberculosis can be resolved into two main components. The first—case finding on an astounding and unprecedented scale—tends to lower mortality. The second—depletion of personnel in sanatoriums^a—results in a reduction of the number of beds available for treatment and thus acts in the opposite direction. The resultant of these components depends on their

magnitude and direction. But only the crudest estimates of these forces are as yet available.

Tuberculosis in the armed services. At present a satisfactory chest x-ray examination is required of all men and women accepted for service with the armed forces.⁷ During the early period of mobilization only three of the nine corps areas x-rayed all the men inducted. Because x-ray photographs were not taken of everyone, it is estimated that between 5000 and 15,000 persons with tuberculosis were taken into the Army during the fall and winter of 1940. This situation rapidly improved, however, and by March, 1941, 51 per cent of all the men called to induction centers received x-ray examinations. Three months later the Adjutant General ordered the inclusion of chest x-ray films of all registrants appearing before induction boards. On January 22, 1942, the order was further modified so that an x-ray examination became a requisite for all applicants for voluntary enlistment as well as for inductees.

As a result of official recognition of the value of the x-ray, tuberculosis case finding has proceeded at a pace hardly believed possible. Many reports of tuberculosis surveys among inductees are now

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available. Rowntree and his associates⁸ found 114 cases of tuberculosis in a group of 19,923 Selective Service registrants between the ages of twenty-one and thirty-six—an incidence of 5.7 per 1000 examined. In a second analysis of 45,585 registrants, aged eighteen to nineteen years, 6.8 cases per 1000 examined were rejected because of tuberculosis.⁹ For Negroes, eighteen and nineteen years old, tuberculosis was tenth as a cause for rejection, the rate being 9.7 per 1000; it was lower in rank for Whites, accounting for the rejection of 6.6 per 1000 registrants. For the age group of twenty years and older tuberculosis was ninth in rank for both Whites and Negroes.

Statistics from the Navy have also been reported.¹⁰ Of a total of 247,253 x-ray films taken at seven Navy training stations and Marine bases, 273 (1.2 per 1000) showed active tuberculosis whereas 786 (3.2 per 1000) were regarded as inactive. Of course, these figures do not reflect the true incidence of tuberculosis, since additional cases, discovered by history and examination, were eliminated at local recruiting centers.

Since Canada has been at war longer than the United States, the experience of the Canadian Army should be of interest. The 14-by-17-inch celluloid film has been adopted by them because of its availability and on the theory that "the cheapest method is the one that is most accurate."¹¹ In one survey of 400,000 men, examined from September, 1939, to March, 1942, 3969, or 1 per cent, were rejected because of tuberculosis.¹² During this same period 114 men developed the disease. Ten of these men had entered the army in the early days before chest x-ray films were required. Of the 104 remaining, 96 had negative induction x-ray films, but 8 had been admitted to the Army, although their initial x-ray films showed small lesions. In another analysis of 328,325 examinations, it was demonstrated that the error in reading films amounted to only 0.003 per cent, since 11 cases of tuberculosis developed in soldiers whose initial x-ray films actually showed lesions but had been interpreted as negative.¹¹ An additional 16 men (0.004 per cent) whose induction x-ray films showed no disease subsequently developed tuberculosis while in the service.

Recognizing that tuberculosis presented a serious threat to the health of the nation, the United States Public Health Service inaugurated its own program shortly after war was declared.^{13, 14} An Office of Tuberculosis Control was established with the following functions and objectives: chest x-ray examination for workers in war industries; chest examination and health education of families in war-industry communities, especially in the underprivileged; chest x-ray examination of Coast Guard recruits; immediate reporting to state and city health departments of men rejected with tuberculosis; and tuberculosis consultation service to state health departments on request.

Two auxiliary projects, of minor importance now but of presumably greater importance in the future, have also been initiated. The first is a routine chest x-ray examination for all admissions to large general hospitals. The second is chest x-ray examination for inmates and employees of state institutions, especially those for mental disease.

To implement this ambitious program, ten portable x-ray units were obtained and set up in trailer automobiles. Each complete unit costs about \$6200 and is staffed with three workers—a physician, a technician and a clerk. Under usual working conditions between three hundred and five hundred photofluorograms (35 mm.) can be taken daily, and the present rate of work for each mobile unit is about two thousand x-ray examinations a week. In co-operation with industry, 250,000 workers were x-rayed in 1942. It is estimated that 1,000,000 examinations will be made in 1943 at a unit cost of 15 cents per examination. Plans for enlarging the program of the Office of Tuberculosis Control did not materialize completely because of failure to obtain an expanded appropriation.

Tuberculosis in industry. Industry has become more cognizant of the role that it can play in eliminating tuberculosis.^{15, 16} In industry it is a combination of several factors that tends to bring about an increase in tuberculosis. The strain of accelerated production under which new workers find themselves causes some breakdowns in those whose lesions are latent or unhealed. Besides, many persons who know they have tuberculosis take the risk to their health and enter industry because of high wages. A third factor is that in the search for employment many persons shift from low-rate tuberculosis areas to areas with high rates, and vice versa. Management has recognized the fact that under wartime stress tuberculosis is likely to increase, but it has been exceedingly difficult to induce labor to establish its own antituberculosis program.

Sawyer,¹⁵ under whose direction the incidence of tuberculosis among employees of the Eastman Kodak Company has been reduced from 2.3 per cent in 1921 to 0.5 per cent in 1941, has presented an "ideal" plan for tuberculosis control: a chest roentgenogram of all present employees; a chest roentgenogram of all applicants for employment; and periodic follow-up roentgenograms of all employees.

Miniature versus regular films. The superiority of x-ray examination over other methods of case finding is admitted by all, but there is still considerable disagreement concerning what procedure is best suited to mass surveys. Excellent reviews of the problem have appeared.¹⁷⁻²² As has been pointed out, the Canadian Army prefers the 14-by-17-inch celluloid film; the United States Army, the 4-by-5-inch or 4-by-10-inch stereo; the United States Navy and Public Health Service, the 35-mm. film. In New York City and elsewhere the 14-by-

17-inch paper film is used routinely. For diagnostic accuracy the 14-by-17-inch celluloid film ranks first, but there is some difference of opinion whether the 14-by-17-inch paper film outranks the 4-by-10-inch stereo. The 35-mm. film is regarded as being on a par with fluoroscopy,¹⁹ but because of its size, it does have some advantages in mass survey work.

Statistical summary. As a result of the almost universal adoption of the chest x-ray examination in both the armed services and industry, it is expected that at least 25,000 new cases requiring hospitalization will have been discovered by the end of 1943.²² Existing sanatorium facilities are pitifully inadequate to absorb the additional load of 25,000 new patients.^{23, 24} Even the most recent statistics⁷ fail to demonstrate the real gravity of the situation because the actual number of available beds in many institutions has been reduced by loss of personnel far below the figures given. Early in 1942 the number of beds for tuberculosis patients in this country totaled 97,726, or 1.62 per death, in 1940 (in 1938 the ratio was 1.41). Minimum standards for hospital facilities require 2 beds per annual death; recommended standards are set at 3. In 1942 only seven states and the District of Columbia met the recommended standards. To care for the burden of the newly discovered cases it is estimated that thirty-two states need from 100 to 6000 additional beds. Massachusetts has a theoretical surplus of 1279 beds above minimum standards to take care of an expected 700 new cases. As has already been indicated, this surplus probably exists only on paper. Many sanatoriums in this state have already been forced by wartime restrictions to reduce the actual number of beds.

TUBERCULOSIS CONTROL IN CIVILIAN LIFE

General hospitals. Recent articles call attention to the fact that the general hospital has not been fully utilized as a source of case finding. In one hospital, routine x-ray examination over a period of eighteen months demonstrated that 4 per cent of the patients had evidence of tuberculous infection and that in 0.6 per cent it was active or questionably active.²⁵

Approaching the problem somewhat differently, Farber and Clark²⁶ analyzed the records of 100 patients consecutively admitted to a general hospital with diagnoses other than tuberculosis and who were later proved to have this disease. Sixty-eight had positive sputums and 3 others discharged tubercle bacilli from extrapulmonary foci. Because of delay or error in diagnosis these patients — a menace to the health of other patients and employees — remained in the hospital a total of 1497 days before transfer to the tuberculosis service. Since 95 of the 100 were pulmonary cases, the value of a routine chest x-ray examination in a general hospital is readily demonstrated.

Nurses and medical students. In view of the fact that unrecognized tuberculosis exists so commonly in hospitals where physicians and nurses receive their training, it is not surprising that it is so serious an occupational hazard for them. The literature pertaining to nurses for the years 1935-1940 has been reviewed by Whitney and Stofer.²⁷ Nurses who spend a portion of their training on a tuberculosis service have a higher infection rate (as measured by the conversion of the tuberculin test from negative to positive) and possibly a higher morbidity rate than those who do not.²⁸ For students of medicine the problem is equally serious.²⁹ Myers and his associates³⁰ compare a group of lawyers with a similar group of physicians and point out that over 7 per cent of the physicians reported having had tuberculosis, whereas less than 2 per cent of the lawyers developed the disease. They show further that since 1936, when a program to protect medical students was adopted, there resulted a gratifying reduction in the number of students infected. Todd³¹ believes: "Annual checking of students and nurses, particularly nurses, is entirely inadequate to properly safeguard health. Tuberculin tests should be made every three or four months and all positive reactors routinely examined by x-ray at the same interval."

Colleges. Lyght³² reports that for the academic year 1940-1941 three hundred and four colleges and universities had tuberculosis programs, an increase of two hundred in four years. There can be no question that in the absence of a definite case-finding program many cases are missed. Lees³³ points out that during 1941-1942 only 11 new cases of tuberculosis were discovered at one hundred and seventy-seven colleges that provided for no case finding (an incidence of 0.07 per 1000 students), in contrast to 744 new cases in three hundred and eleven colleges with such a program (an incidence of 1.3 per 1000). Available reports indicate that the infection rate in colleges has declined 30 per cent.

Extrafamilial contacts. A valuable paper by Twinam and Pope³⁴ calls attention to the fact that failure to find the source of infection within a household should only serve as a stimulus for added search among the extrafamilial contacts.

County accreditation. Hailed as a "new idea in human tuberculosis control," county accreditation applies to human beings some of the technics used in eliminating tuberculosis from cattle. The plan, initiated in Minnesota, consists of awarding certificates to those counties where reasonable success has been obtained in finding and controlling tuberculosis according to established standards. Details are to be found in an article by Myers,³⁵ but briefly the standards require an average death rate of 10 or less per 100,000 population and a tuberculosis infection rate, as evidenced by a positive tuberculin test, of less than 15 per cent among high-school seniors. At least seven of Minnesota's eighty-seven

counties have already been accredited. A worthwhile step has been taken.

Simplified procedures. Case finding is "big business"³⁶ and, as has been pointed out, mass surveys have received great impetus from the war. Because of the increased volume of the work, unproductive tasks must be eliminated. Simplified procedures employed in New York City include, among other things, abbreviated history taking, elimination of routine physical examination and interpretation of x-ray films according to an established code.

CHEMOTHERAPY AND VACCINES

The discovery of the sulfonamides has led to a search for related chemicals that might be of value in the treatment of tuberculosis. The zeal of the bacteriologists hunting for a vaccine is a match for the fervor of the chemists. Chemicals and vaccines have been found—but, although they appear to be of some usefulness in the laboratory, their worth in the clinic must still be demonstrated. Skepticism in the evaluation of experimental research is a sound attitude; cynicism is not.³⁸

Chemotherapy. The sulfones have displaced the sulfonamides in interest.^{39, 40} The in-vitro action of these chemicals in inhibiting growth of tubercle bacilli roughly parallels their therapeutic effects in guinea pigs.³⁸ Up till now promin, the sodium salt of *p, p'*-diaminodiphenylsulfone-*n, n'*-didextrose sulfonate, has been subjected to the greatest amount of study. It is definitely established that promin has a deterrent effect on tuberculosis in guinea pigs,^{41, 42} and even when the experimental tuberculous process has already developed it can be resolved under the influence of this chemical.⁴³ Some guinea pigs, with the aid of promin therapy, develop such a high degree of immunity to tuberculosis that no macroscopic evidence of the disease can be found a year or more after therapy is discontinued.⁴⁴ Inhalation of nebulized promin is said to be even more effective than when the drug is given by mouth.⁴⁵

Human experiments with promin are less encouraging. Given by mouth to 32 patients, the drug was more toxic than for guinea pigs and it appeared incapable of sterilizing the body of tubercle bacilli.⁴⁶ When it was given by the massive intravenous-drip method,⁴⁷ no beneficial effect was observed in 12 patients treated. British investigators⁴⁸ have had some success in treating laryngeal tuberculosis by applying promin locally and believe that further experiments are warranted.

At present other derivatives of diaminodiphenylsulfone are coming under investigation.⁴⁹ Of these, disodium formaldehyde sulfoxylatediaminodiphenylsulfone has been found to be less toxic for guinea pigs^{50, 51} and appears to be of some promise. Research at the National Institute of Health indicates that phosphoryl derivatives should be investigated more thoroughly.⁵²

Vaccines. Vaccination for the prevention of tuberculosis is by no means a new idea.⁵³ The only justification for taking this topic up is that two recent attempts at developing a safe and reliable vaccine appear worthy of mention.

Steenken and Gardner⁵⁴ have used the living avirulent bacterial dissociates of five different strains of tubercle bacilli in an effort to enhance the low resistance of the guinea pig to tuberculosis. They found that the immunity of guinea pigs, as determined by the subsequent inoculation of a virulent strain, could be increased. They believe that they have obtained proof that the avirulent dissociate is not devoid of antigenic properties and that immunity may not be type specific.

Potter^{55, 56} has approached the vaccine problem somewhat differently. He noted that whereas tubercle bacilli may remain alive for two or more years under high vacuum when stored dry, they are readily killed at body temperature in the absence of oxygen if sufficient moisture is present. His technic is to give the tubercle bacillus an environment where its metabolic needs are high and at the same time deprive it of an essential constituent—oxygen. In this way Potter demonstrated that tubercle bacilli gradually die off and that all the bacilli are dead after one month's incubation in the moist state at 38° C. and under a high vacuum. By this method an avian strain (P₄) was prepared as a vaccine, and the virulent organism itself was used for subsequent tests in rabbits. A greater degree of immunity was conferred on the experimental animals than had been obtained with any of the earlier vaccines used. But since the immunity was incomplete, other studies are now in progress to improve the method of vaccination.

SURGERY

Current trends in collapse therapy have been analyzed by Drolet.⁵⁷ Summarizing a five-year (1937-1941) survey of one hundred and one Canadian and American hospitals with a total bed capacity of 33,050, he found that about 50 per cent of all patients were given some form of collapse treatment. Apparently the number of patients receiving artificial pneumothorax was stabilized during this period, but the number of phrenic nerve operations decreased 8 per cent. On the other hand, there was a 34 per cent increase in the number of intrapleural pneumolyses. About 4 per cent of the patients in sanatoriums were subjected to thoracoplasty in 1941 and, compared with 1934, there was a four-fold increase in the number of patients who had this operation. In the New England states the ratio of patients subjected to thoracoplasty has increased from 56 to 89 per each 1000 patients. But, as Davidson⁵⁸ and Churchill and Klopstock⁵⁹ point out, analysis of current trends has but a limited usefulness as a guide to therapy in a field as rapidly advancing as thoracic surgery.

The treatment of pulmonary tuberculosis complicated by tracheobronchial disease is a specific problem that continues to be the subject of considerable debate. Myerson,⁶⁰ who believes that tuberculosis of the bronchus and trachea has a good prognosis, regards pneumothorax as "superfluous once a bronchial lesion develops." Salkin and his co-workers,⁶¹ on the other hand, favor the use of collapse treatment except in cases complicated by bronchial stenosis. Their conclusion is, "Some of our best results of bronchitis have followed the use of pneumothorax and thoracoplasty." Unfortunately by placing in one category those cases treated by pneumothorax and those treated by thoracoplasty, these authors have evaded one of the most controversial aspects of the entire problem. Both procedures—pneumothorax and thoracoplasty—must be analyzed independently if there is to be any clarification of the disputed issues.

Considerable light was thrown on the subject of tracheobronchial tuberculosis in a recent symposium.⁶²⁻⁶⁴ The consensus is that the presence of tuberculous bronchitis greatly complicates the treatment of the pulmonary lesions. Pneumothorax gives poor results and, when it is ineffective, it is worse than "superfluous," for it encourages complications, such as empyema and unexpanded lung. In cases of definite stenosis, neither pneumothorax nor phrenic nerve operations are as effective as thoracoplasty. The advantages of thoracoplasty can be summed up as follows: it is the safest procedure, atelectasis seldom results, infection of the pleural space is rare, and late suppurative changes within the lung are prevented.

According to Rafferty and Shields⁶⁵ pneumothorax is to be condemned in the presence of bronchial stenosis, for it causes interference with bronchial drainage and encourages atelectasis. They advocate the following plan of management when bronchial disease is discovered: attention should be centered mainly on the bronchus rather than on the pulmonary lesion; the idea of collapse treatment should be abandoned, at least temporarily; early treatment should consist of a longer than average trial of bed rest; artificial pneumothorax may be cautiously attempted if the bronchial disease appears to be slight; and thoracoplasty, in most cases, is preferable to pneumothorax.

From a purely theoretical standpoint lobectomy and pneumonectomy may be the procedures of choice when stenosis complicates the usual forms of treatment. That resection of a lung is practical as well as theoretical is being borne out by a gradually accumulating mass of evidence. In a group of 12 cases reported by Benedict,⁶⁶ one lobectomy and three pneumonectomies were done. Of the pneumonectomies, one was done after an unsuccessful thoracoplasty. There was only one death, and that was due to subsequent extension of the disease in the contralateral lung. Behrend⁶⁷ points out that

pneumonectomy should be limited to those cases in which there is chronic ulcerative tuberculosis of the bronchus with ipsilateral pulmonary disease.

The number of lobectomies done for tuberculosis is gradually increasing. Drolet⁶⁷ reports that there were only 9 done in 1937 but 14 in 1938, 16 in 1939, 25 in 1940 and 28 in 1941. The rationale for lobectomy is clearly outlined by Churchill and Klopstock.⁶⁸ Lobectomy and pneumonectomy are procedures distinctly different from one another, each with its own set of indications. Pneumonectomy is not an alternative to collapse therapy since it is both irreversible and nonselective. On the contrary, lobectomy is highly selective and is more conservative of pulmonary function than a seven-rib thoracoplasty. A lobectomy may be considered as an alternative to artificial pneumothorax when there has been irreparable destruction of lung substance. Lobectomy shortens the span of treatment, maintains (better than thoracoplasty) the integrity of the thoracic cage, and removes the offending lesion. If, after bed rest and pneumothorax treatment, "there is good reason to believe that the therapeutic goal of a re-expanded lung, with a closed lesion, cannot be achieved within a reasonable length of time, lobectomy may be considered."

MINOR NOTES

Pregnancy. Although pregnancy is an added burden to a woman with tuberculosis, the current trend is toward less interference with the pregnancy and more treatment of the tuberculosis. Interruption of pregnancy is being advocated less and less.⁶⁸

Two recent papers are especially deserving of mention. One report concerns a group of 86 women, eighteen to thirty-nine years of age, whose pregnancy was allowed to go to full term.⁶⁹ Of these, adequate follow-up on 82 revealed that only 15 (18 per cent) were dead, in contrast to 39 per cent deaths for all women of the same age group discharged from the sanatorium for the first time during the same period (1921-1940). No explanation is advanced for the puzzling statistical conclusion that the death rate of all women between the ages of eighteen and thirty-nine is double that of the pregnant group. The authors remark conservatively that "while this group is too small to warrant definite conclusions . . . it seems to indicate that when tuberculosis is properly treated pregnancy probably does not adversely affect the tuberculous process."

The second paper is that of Lyman,⁷⁰ who made an intensive study of 1818 women discharged from the Gaylord Farm Sanatorium. In order to determine the effect of marriage and pregnancy on the course of the disease he divided his patients into three groups—single, married and later married. Follow-up studies revealed that of 782 married women 41 per cent were dead and that of the 721 single women 51 per cent were dead.

prisingly, there were only 40 deaths (13 per cent) of the 315 later married. In this group, if reactivation of the disease occurred at all, it did so without exception during pregnancy or within three months post partum. In the light of Lyman's statistics, advice against marriage to a young woman with arrested tuberculosis appears, on the whole, unjustifiable.

The need for the routine inclusion of chest x-ray examination in prenatal clinics and lying-in hospitals cannot be urged too strongly. Recent evidence proves that ten times as many cases of active tuberculosis can be found in those hospitals where routine x-ray screening is done than in those hospitals where no such program exists.⁷¹

Anatomy of the tubercle bacillus. The electron microscope has helped to elucidate some of the controversial details concerning the structure of the tubercle bacillus, since it allows for full resolution of an object at magnifications up to 100,000. One disputed point—the question of the capsule—has been settled. Electron photographs show that a membrane or capsule is uniformly present and that in some instances it contains granules.⁷²

New technics. By the use of fluorescent microscopy tubercle bacilli can be demonstrated with greater rapidity and with a greater number of positive tests than by the use of ordinary staining technics.⁷³

The chorioallantoic membrane of the chick embryo can be made to serve as a reliable rapid culture medium for the differentiation of tubercle bacilli, especially regarding degrees of virulence. Within six days after implantation of suspensions of bacilli, 96 per cent tubercle formation was present in the membranes implanted with a virulent strain, in contrast to only 18 per cent tubercle formation in those implanted with a closely related but avirulent strain.⁷⁴

Serum albumin and globulin, as determined by electrophoresis methods, show changes that parallel the clinical course of tuberculosis, both in experimental animals and in human beings.⁷⁵

Ascoli,⁷⁶ in transplantation experiments on calves, has brought forth evidence to show that presence of an active tuberculous nodule enhances resistance to tuberculosis. Further work along the lines suggested by his research should be of considerable interest.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30021

PRESENTATION OF CASE

First admission. A seventy-year-old retired dentist entered the hospital because of swelling of the legs.

The patient had been in excellent health until the age of sixty-five, at which time he had several episodes of hemoptysis. Sputum examination and x-ray films of the chest were positive for tuberculosis. He spent thirteen weeks in a sanatorium, and was sent home without any further signs or symptoms. From that time on he had been bothered by "gas in the stomach."

About six months before admission the patient noticed the insidious onset of edema of the lower extremities, which progressed and extended up to the midcalf. This was associated with a sense of uneasiness and tiredness in the legs, but there was no pain, and no dyspnea or orthopnea. He had lost about 9 pounds but believed that this was due to the change in his life consequent to his wife's death.

Physical examination showed a well-developed, poorly nourished man, with sacral edema. The thoracic wall was deformed, the sternum being thrust anteriorly and rotating to the right. The cardiac border could not be made out, but the sounds were of good quality and regular. There was slightly diminished resonance throughout the right lung, but no rales were heard anywhere.

The blood pressure was 190 systolic, 100 diastolic. The temperature was 98.6°F., the pulse 72, and the respirations 20.

Examination of the blood showed a red-cell count of 3,880,000, with a hemoglobin of 12.2 gm. per 100 cc. The white-cell count was 18,200, with 86 per cent neutrophils. Urine examination showed a specific gravity of 1.015, a + test for albumin, and rare red and white cells. A blood Hinton test was negative. The blood sugar was 61 mg. per 100 cc., the nonprotein nitrogen 32 mg. A phenolsulfonephthalein test gave 20 per cent excretion in fifteen minutes, with a total of 60 per cent at the end of two hours.

X-ray examination of the chest showed a hazy and linear density throughout the right upper lung

**On leave of absence.*

field. Linear, sharply defined areas of increased density were seen throughout both midlung fields. The diaphragm was low in position, with limited expiratory motion. A Graham test was negative. A gastrointestinal series was noncontributory. A electrocardiogram showed normal rhythm, a rate of 70 and slight slurring of R₂. The ST segments in Leads 1, 2 and 4 were slightly concave, suggesting digitalis effect. The T waves were low throughout. There was sinus arrhythmia. The patient was discharged at the end of six days with a diagnosis of nutritional edema.

Second admission (three months later). After discharge, the patient placed himself on a regime of essence of peppermint, sodium bicarbonate and luminal, with considerable relief of his stomach distention. He also took 1½ gr. of digitalis daily. The swelling of the legs increased and involved the thighs and hips. During the week before admission he noted decrease in acuity of close vision, dullness of his sensorium and a general feeling of inadequacy. There had been considerable itching of the skin and some gain in weight.

Physical examination showed marked boggy and pitting edema, extending up to the lower border of the scapulas. There was some scrotal edema. Scattered, fine, crackling rales were heard over the upper right chest anteriorly and posteriorly, with dullness in the right upper chest anteriorly. The examination was otherwise the same as previously.

The blood showed a red-cell count of 4,060,000 and a white-cell count of 7700, with 65 per cent neutrophils. The urine had a specific gravity of 1.014 but was otherwise negative. The nonprotein nitrogen was 30 mg. per 100 cc., and the blood protein 6.3 gm., with 4.0 gm. of albumin and 2.3 gm. of globulin — an albumin-globulin ratio of 1.7.

The patient continued to take digitalis daily. On the third hospital day he was given 1 cc. of Mercupurin intravenously. His urinary output was between 1750 and 1250 cc. on an intake of about 1400 cc. daily. A phenolsulfonephthalein test on the fourth hospital day gave 10 per cent excretion in fifteen minutes, and a total of 40 per cent at the end of two hours. The nonprotein nitrogen was normal. On the fifth hospital day the urine showed a +++ test for albumin and contained many red cells which persisted for almost three weeks. During the second week the temperature ranged between 100°F. and 102°F.; the pulse was about 80, and the respirations 25. Cultures of the blood and urine were negative. An intravenous pyelogram performed on the tenth hospital day showed a normal outline of the left kidney. Several calcified nodes were seen overlying the left kidney. The kidney and pyelogram outlines on the right were not visualized. Intravenous dye appeared promptly on the left side. The left calyces and pelvis were incompletely visualized but were not grossly abnormal. The right calyx

were not well seen. The right lower calyx was enlarged and deformed. The examination was not entirely satisfactory. A cystoscopy on the twentieth day revealed bloody urine in the bladder, from which a handful of clot was removed. There was slight trabeculation; both ureteral orifices were normal, and clear urine was seen coming from both. The prostate was enlarged, but no masses could be felt in the pelvis. A retrograde pyelogram showed the right superior and inferior calyces to be separated, and there was a questionable filling defect. One of the right middle calyces was somewhat blunted, and the kidney appeared enlarged. The left kidney and pelvis were normal.

The patient was given one transfusion of blood and received a high-calorie, high-vitamin diet. His condition improved considerably after the first three weeks; the hematuria subsided, the edema disappeared, and he was discharged eight weeks after admission.

Third admission (two months later). The patient had felt well for the first four weeks and then developed a dull aching pain in the right flank, which became progressively severer. Standing seemed to aggravate it. He had nocturia four or five times but no other urinary symptoms. During the ten days prior to admission he had two attacks of vomiting. In the second one, the material was described as "catsup colored." He had swelling of the legs on two occasions. He thought that he had lost about 6 pounds during this period.

Physical examination showed soft pitting edema of both ankles, with scaling of the skin. The lungs were clear. The heart was of normal size. The sounds were regular and of good quality. There was an occasional dropped beat. A rather firm, movable, tender mass was palpated in the right flank, which shifted slightly, if at all, with respiration. The mass was the size of a grapefruit, and its upper border disappeared under the costal margin. Many dilated veins extended over the abdomen to the lower thorax.

The blood pressure was 100 systolic, 40 diastolic. The temperature was 98°F., the pulse 80, and the respirations 20.

Examination of the blood showed a red-cell count of 3,510,000, with a hemoglobin of 70 per cent. The white-cell count was 9600, with 71 per cent neutrophils. The urine showed a + test for albumin and occasional red and white cells; the specific gravity was 1.018. The blood sugar was 111 mg. per 100 cc., and the nonprotein nitrogen 34 mg. The blood chloride was 99.9 milliequiv. per liter, and the carbon dioxide combining power 22.5 millimols per liter. The blood protein was 7.2 gm. per 100 cc. Two cultures of the urine were negative; one showed moderate numbers of nonhemolytic streptococci, two showed *Staphylococcus albus*, and one showed colon bacilli and enterococci.

Retrograde pyelograms failed to define the outline of the right kidney accurately, but it appeared to be

enlarged. There was upward displacement of the upper part of the ureter, without lateral displacement. All the calyces were somewhat enlarged, irregular and blunt. There was considerable anterior displacement of the right ureter. Several non-opaque filling defects were seen in the calyces, which were interpreted as stones or blood clots. X-ray films of the chest taken about eight months after the first films showed progression of the process, especially in the base and the lateral aspect of the left lung field. The process consisted of flecky and streaky areas of increased density in the central and lateral lung fields. Several areas of increased density were apparent in the region of the left base, as well as a triangular dense shadow close to the right hilus.

The patient was discharged at the end of the fourth week without apparent change in his condition.

Final admission (four months later). For about two months the patient remained the same. An x-ray film of the chest during this period showed further progression of the pulmonary process. The lesions had a more sharply outlined and nodular appearance than formerly. He developed progressive shortness of breath and cough. The abdomen increased in size. Breathing became progressively more difficult.

Physical examination showed a pale, emaciated man in marked respiratory distress. There was dullness anteriorly over the right lower lobe, with decreased breath sounds and definite egophony. Scattered rales were heard over both lower lobes. The abdomen was grossly distended, and there were many large and prominent veins.

The blood showed a red-cell count of 3,820,000, with 10.7 gm. of hemoglobin. The white-cell count was 6600, with 76 per cent neutrophils. The urine was negative. An abdominal paracentesis yielded 5000 cc. of greenish fluid, with a specific gravity of 1.016 and a protein content of 2.2 gm. per 100 cc. Following the tap, there was marked relief of the respiratory distress, and a large, firm, nodular mass was palpable in the right upper quadrant. X-ray studies of the chest showed questionable fluid in the right pleural cavity.

The patient's condition gradually became worse, and he died on the tenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JOSEPH C. AUB: May we see the x-ray films?

DR. LAURENCE L. ROBBINS: The gastrointestinal films simply show anomaly in position. So far as the chest is concerned, I believe that there is definite evidence of tuberculosis in the right apex. There is something more, however — a diffuse linear process involving both lungs. These films were taken at the time of the original admission. After an interval of about eight months, the appearance of the chest changed considerably. In addition to what was previously present, there are now definitely round

shadows. These shadows I believe are superimposed on the other process. This shadow here is what raised the question of fluid, and I should think that it is perfectly consistent with fluid in the right pleural cavity.

So far as the intravenous pyelograms are concerned the majority of films were unsatisfactory. This retrograde pyelogram was done eight months after the first admission and is the one from which most information was obtained. Of greatest significance is the fact that the lower pole of the kidney is obscured and not seen, but I cannot visualize a definite mass. There is elongation of the two lower calyces, with displacement of the ureter forward.

DR. AUB: In the diagnoses we must place an old one — pulmonary tuberculosis — and sclerosis of the aorta, because of hypertension and a distortion

vena cava in a progressive manner. The normal blood protein of 6.3 gm. also fits in with the idea that obstruction may have been the cause of the edema. The next diagnosis that one has to make is a retroperitoneal tumor mass in the region of the right kidney. It may have originated from the kidney or from the adrenal gland, or it may have been a primary retroperitoneal tumor. I think that one must arrive at the conclusion that the mass was a metastasizing neoplasm, since the masses shown in the x-ray film of the chest are suggestive, although not typical, of metastatic neoplasm rather than of tuberculosis. The only other diagnosis I can make is tuberculosis of the kidney. The patient had hemorrhage from the kidneys, which suggests tuberculosis, and we know that he had pulmonary tuberculosis. If it were tuberculosis of the kidney, I should ex-

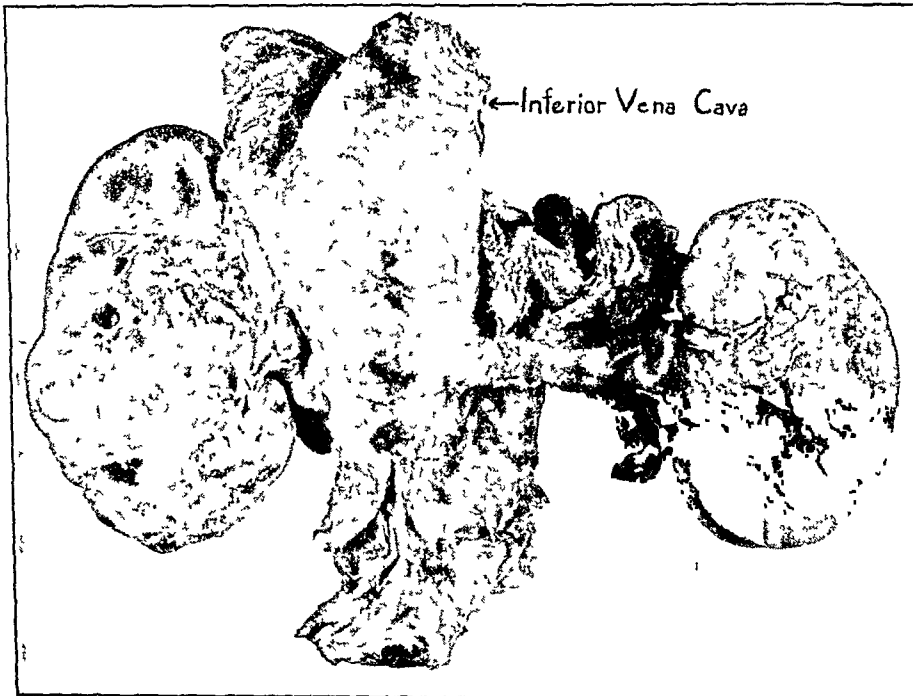


FIGURE 1. Renal-Cell Carcinoma of Right Kidney with Extension into Both Renal Veins and Inferior Vena Cava.

of the chest, with change in the position of the heart. Incidentally, this man was seventy years old and I have no desire to make a single diagnosis. The older the patient, the more diagnoses he rates.

Then we come to the mass in the abdomen, which may have several interpretations. The stomach was displaced, which Dr. Robbins says was a congenital anomaly; but it also might have been due to the mass displacing it. From the beginning there was evidence of obstruction to the vena cava. First there was edema, then increased venous flow in the abdominal wall with many superficial veins; so whatever was present in the abdomen obstructed the

pect, but not insist, that there would have been evidence of tuberculosis in the bladder. The only suggestion of anything wrong with the bladder is the slight trabeculation. Extrarenal tumors are of various types — sarcomas, neurofibromas, fibromas, adrenal-rest tumors and cysts; but none of these appeal to me because the lesion is obviously in the kidney, particularly in the calyces, pushing the ureter forward and obstructing it. Does this film suggest obstruction?

DR. ROBBINS: I do not believe that there is much obstruction by the process; the ureter is displaced forward.

DR. AUB: So we come to the diagnosis of the type of neoplasm of the kidney. Now, I leave an area of relative security and plunge into a less secure one. This may have been a hypernephroma in which there was a hemorrhage, as evidenced by bleeding. If it were a hypernephroma I should expect to have seen more definite snowball-like lesions in the x-ray films of the chest. Somehow I rather suspect that this lesion was more in the hilar region of the kidney, and when tumors are primarily located there they are usually papillary epitheliomas. That is the diagnosis which I think is more likely to be made, although these tumors are less frequent than the hypernephromas. I believe that it broke through, grew outside the kidney and pushed the ureter to an anterior position, with a good deal of growth behind the kidney. From the description the ureter was probably involved, although I do not believe that I can make that diagnosis from these x-ray films. It also produced obstruction of the vena cava and pushed the duodenum over. These tumors may also have pulmonary and bone metastases. I do not believe that this was renal tuberculosis.

The patient was discharged eight weeks after the second admission. Why they did not operate then I do not know, but I suspect that it was because of the x-ray films of the lungs.

DR. FLETCHER H. COLBY: I saw the patient during his second admission. It is not quite clear from the history that the patient was in a critical condition even at that time. When it was considered whether to cystoscope the patient, Dr. Dwight Siscoe wrote in the record, "It might be considered unwise by some to put him through a retrograde pyelogram but to me it seems to be either that or just sitting back and waiting until he dies." In other words, the patient was in extremely poor condition even as early as the second admission. At that time there were dilated veins in the abdominal wall. We suspected that the bleeding, which was gross and copious, might have been due to the Mercupurin. It seemed to me, however, that there was probably some other cause, such as a bladder tumor. The patient was cystoscoped, and the bladder was normal except for some trabeculation, which is evidence of mild obstruction rather than of tuberculosis. At the time of discharge it was thought that the patient probably had a malignant tumor of the right kidney, with obstruction to the vena cava. The question of operation was never seriously raised because he was in such poor shape and because operation offered him nothing. It is interesting that he had 4600 units of radiation with the 200-kilovolt machine during the last admission and temporarily improved a great deal.

CLINICAL DIAGNOSIS

Retroperitoneal tumor.

DR. AUB'S DIAGNOSES

Papillary epithelioma of pelvis of right kidney, with extension producing obstruction of the vena cava and with metastases to lungs.
Pulmonary tuberculosis.
Sclerosis of aorta.

ANATOMICAL DIAGNOSES

Renal-cell carcinoma of right kidney, with extension into both renal veins and the inferior vena cava and with metastases to lungs, liver and right adrenal gland.
Pulmonary tuberculosis.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: From this photograph (Fig. 1) you can see that the right kidney was replaced for the most part by a large tumor, but the most striking thing was this large mass between the two kidneys. The inferior vena cava measured 6 cm. in diameter and was filled with tumor thrombus. This tumor extended into the right renal vein, which was practically obliterated and shortened by the tumor, and then into the vena cava. Other interesting findings were that the left renal vein contained two movable tumor thrombi and that there were metastases to the left kidney. The right adrenal gland was completely replaced by tumor. This tumor thrombus in the vena cava had extended down into both iliac veins and had produced partial obstruction.

The tumor was a hypernephroma or what we prefer to call renal-cell carcinoma. The tumors of the renal pelvis are usually papillary tumors that extend down the ureter. I have never seen one invade the renal vein or extend into the vena cava. The renal tumor that usually invades the vena cava is the renal-cell carcinoma which arises from the parenchyma; the other tumors that are prone to do that are the hepatomas and the carcinomas of the adrenal cortex. The lungs showed numerous metastases as well as active tuberculosis. It is interesting that the tumor thrombus in the inferior vena cava extended up to the liver and also into the hepatic veins and had produced metastases to the liver.

DR. AUB: How about the bones?

DR. CASTLEMAN: They contained no metastases.

CASE 30022

PRESENTATION OF CASE

A seventy-two-year-old white widowed domestic entered the hospital because of swelling of the abdomen and legs of four weeks' duration.

The patient was well until about four to five weeks before admission, when she noted the onset of swelling of the abdomen and ankles. At about the same time she developed a cough and a slight . . . There were oliguria and darkening . . .

She experienced loss of strength and appetite, dyspnea on exertion and easy fatigability. She had had no pain, change in bowel habits, dysuria, nausea, vomiting, hematemesis or jaundice. She was not certain whether she had recently had one or two clay-colored stools.

Fourteen years before admission the patient had a secondary syphilitic rash, with a positive dark-field examination for spirochetes. She was treated for two years, and the blood became seronegative after the first eight months.

Physical examination showed a poorly nourished, thin woman in no discomfort. The skin was slightly icteric, with numerous superficial varicosities of the legs and occasional varices of the lower abdomen. There was soft pitting edema of both legs to the knees. A few fine crackles were heard at the left base. No definite cardiac enlargement could be made out. There was a moderately harsh, blowing precordial systolic murmur, heard best in the pulmonary and parasternal areas. The sounds were regular and of good quality. The abdomen was protuberant, with a fluid wave and shifting dullness. The liver was percussed two fingerbreadths below the costal margin; it was not palpable. One examiner thought there was a large mass rising from the pelvis to the umbilicus and attached to the uterus.

The blood pressure was 138 systolic, 80 diastolic. The temperature was 98.6°F., the pulse 80, and the respirations 18.

Examination of the blood showed a red-cell count of 4,470,000, with 11 gm. of hemoglobin. The white-cell count was 11,000, with 80 per cent neutrophils. A blood Hinton test was negative. The urine had a specific gravity of 1.026 and gave a + test for bile; the sediment of a catheterized specimen contained 5 to 15 white cells and 15 to 20 red cells per high-power field. The stools were yellow, watery and guaiac negative. The nonprotein nitrogen was 20 mg. per 100 cc., and the protein 5 gm. The direct van den Bergh was 1.8 mg. per 100 cc., the indirect 2.5 mg. The prothrombin time was 29 seconds (normal, 16 seconds). The hematocrit was 44.5. A cephalin flocculation test was ++ in twenty-four hours and +++ in forty-eight hours.

An intravenous pyelogram was negative. On x-ray examination there was a large, soft-tissue mass, probably an enlarged uterus, filling almost the entire pelvis and pressing on the roof of the bladder. A gastrointestinal series and a barium enema were negative except for the presence of fluid in the peritoneal cavity. No esophageal varices were seen. X-ray films of the chest showed some linear areas of atelectasis at both bases, probably due to abdominal ascites. The lung fields were otherwise clear. The heart was transverse in position but not greatly enlarged.

The patient's condition improved slightly during the first week. The urine cleared almost completely, and there was no bile. Abdominal paracentesis on

the sixth day yielded 6 liters of clear, straw-colored fluid; no tumor cells were seen. Peritoneoscopy showed a large, round, rather hard, white mass, approximately 15 cm. in diameter, in the pelvis. The liver edge was irregular and nubby but of normal color. There was no evidence of tumor metastases.

Although there was a moderate degree of drainage through the peritoneoscopy incision, the fluid seemed to reaccumulate in the next four to five days. On the fifteenth hospital day the patient became drowsy and irresponsive. She was given daily intravenous fluids with vitamins. The prothrombin time was 30 seconds (normal, 20 seconds). The hematocrit was 39.7, and the nonprotein nitrogen 18 mg. per 100 cc. The blood chloride was 105.5 milliequiv. per liter, and the carbon dioxide combining power 20.4 millimols per liter. The following day the patient became comatose. Examination was essentially as before, except for a fetid, somewhat mousy breath and hyperactive tendon reflexes and knee jerks. The urine gave a + test for albumin and a ++ test for bile, and contained innumerable white cells. A culture gave many colonies of colon bacilli. The nonprotein nitrogen, however, was only 16 mg. per 100 cc. She remained in coma and died on the twenty-fifth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. FRANCIS D. MOORE: This is the story of a previously well seventy-two-year-old woman who over a four-week period, developed evidence of obstruction of the portal vein and of the veins of the legs, became acutely ill, passed into coma with jaundice, and died. To this train of events we have added a pelvic tumor and some evidence of infection of the urinary tract. The relation of the latter two to the main train of events is not too clear. The patient's story suggests the gradual onset of a systemic disease, probably due to visceral damage, with few localizing symptoms but with loss of weight, strength and appetite, dyspnea and fatigability. The only localizing factor that we have is the questionable story of clay-colored stools and the development of jaundice.

The fact that fourteen years ago she had a secondary syphilitic lesion may have some bearing on the present trouble. The treatment, however, sounds adequate. She became seronegative at that time and on admission had a negative Hinton test, so for the moment I shall disregard syphilis.

On entry the skin showed superficial varices of the legs and lower abdomen, which may have been the telangiectatic type of varices that one sometimes sees in parenchymatous disease of the liver. The edema seemed to be confined to the legs. No cardiac enlargement could be made out, and this, together with the x-ray findings, the other physical findings and the essentially normal blood pressure, tends to rule out heart disease as the fundamental lesion. Another

sion that in a person of this age could well be of great importance is chronic pyelonephritis. She had red and white cells in the urine, as well as albumin. Since the urine concentrated, however, to 1.026 and since she never showed an elevation of the non-protein nitrogen I think it is best to regard these urinary findings as due to a colon-bacillus cystitis, probably associated with the pelvic tumor, which was pressing on the bladder and probably altering its function.

The physical findings pertaining to the liver are highly significant. She was slightly icteric, she had fluid wave, and the liver was apparently enlarged. To go with this, there was bile in the urine and a van Bergh of 2.5 mg. indirect and 1.8 mg. direct. A proportion of direct to indirect bilirubin of less than 1 per cent is strongly against an extrahepatic cause of jaundice. In other words, obstruction of the common bile duct usually produces a percentage of direct to indirect bilirubin that is 75 per cent or higher. The range of this proportion does not definitely indicate parenchymatous liver disease as its source but it certainly is strongly suggestive. Low percentages of direct to indirect bilirubin are usually associated with hemolytic processes. We have no evidence for that here, as the red-cell count was in the normal range.

The prothrombin time was almost twice the normal, which certainly is also suggestive of liver disease. Furthermore, we see later that she received daily intravenous infusions with vitamins and that the prothrombin time became 30 seconds, with a normal of 20 seconds. Owing to the facts that most intravenous vitamin mixtures used in this hospital at the present time contain vitamin K or one of its precursors and that after receiving these vitamins intravenously she still had an elevated prothrombin time, we have here further excellent evidence that this patient had severe liver damage. As a matter of fact, the response of the prothrombin time to parenterally administered vitamin K is an excellent index of liver function, and this patient apparently showed no response at all. Fitting in with this concept is the cephalin flocculation test, which was +++ in forty-eight hours. The finding of 6 liters of clear straw-colored fluid in the abdomen is simply a part of this picture, the result presumably of portal obstruction. The serum protein of 5.0 gm. per 100 cc. is probably also an expression of hepatic failure, and the edema in the legs could have been due to this factor, although we do not necessarily see peripheral edema with a serum protein of 5.0 gm. She had a pelvic tumor, however, and with a local fault to aggravate the situation, edema progresses rapidly.

Peritoneoscopy showed a liver edge that was irregular and nubby but of normal color and there was no evidence of tumor metastases. This, I think, fits in perfectly with the concept that we are dealing here with diffuse liver damage, such as portal cir-

rhosis or possibly the end results of an earlier subacute hepatitis.

The peritoneoscopy also showed a 15-cm., white, round, large, hard tumor in the pelvis. We have no way of knowing whether it was connected with the uterus or with the ovaries or whether it had nothing at all to do with the reproductive organs. The patient was seventy-two years old and this makes any intrauterine lesion except an endometrial adenocarcinoma extremely unlikely, and yet for an adenocarcinoma of the endometrium to present a large, round, white mass in the pelvis would be most exceptional. Tumors of the ovary, however, frequently give this picture. In a woman of this age most of the common benign and malignant tumors of the ovary may be found. The surface of this tumor was not papillary and there were no implants on the liver or the peritoneum, and no tumor cells in the abdominal fluid, which makes papillary or pseudomucinous cystadenocarcinoma of the ovary moderately unlikely. It could be a large fibroma of the ovary, and with the abdominal fluid, one might think that the fibroma was responsible for the abdominal fluid. We find that she has no fluid in her chest, however, and although this does not rule out fibroma of the ovary, it makes it less likely as a cause for the tremendous amount of abdominal fluid. Other ovarian tumors, including carcinoma of the ovary, can give tremendous amounts of abdominal fluid and even chest fluid without implants and without tumor cells in the fluid. The mechanism of fluid collection in such cases must be in some way related to that in the fibroma group. Therefore, we cannot say with certainty that the ovarian tumor in this woman was not responsible for the fluid collection. But with so much evidence of liver damage, I should think that the ovarian tumor was an incidental and secondary finding, so far as the general trend of this woman's disease and her death are concerned.

After she had been in the hospital for a time, she became comatose and developed a somewhat mousy breath and changes in her reflexes. The mousy breath is classically supposed to be an accompaniment of terminal liver damage. One wonders if this could be due to abnormal circulating amounts of acetamide and related compounds, which, in the purified state, smell like mouse feces.

I am unable to interpret the reflex changes. They could possibly be associated with cerebral thrombosis, a not uncommon terminal event in people of this age, no matter what the underlying pathologic process that is responsible for the depleted condition.

We therefore come down to the diagnosis of liver failure. Owing to the fact that she had massive ascites before the appearance of much jaundice, I think that she had portal cirrhosis rather than biliary cirrhosis associated with either cholangitis or obstruction of the bile ducts. The fundamental etiology for a portal cirrhosis is not clear from the

history. No mention is made of alcoholic intake, and there is nothing to suggest that she had sub-acute hepatitis in the past due to toxins other than alcohol.

Did she have a hepar lobatum? This is a late anatomic lesion due to tertiary syphilis in the liver, and in so far as it is an irreversible pathologic change, it can exist in the presence of a negative serologic test. The peritoneoscopic picture, however, was not that of hepar lobatum, and I should not expect that a patient would have liver failure of this degree on the basis of a hepar lobatum.

I am considering the ovarian tumor to be incidental because the only way in which it could produce this picture would be by liver metastases, for which we have no evidence. I shall make the reservation, however, that the ovarian tumor could have had something to do with the collection of fluid both in the abdomen and in the subcutaneous tissues of the legs. The likeliest solid, round, hard, white tumor of the ovary in a woman of this age is probably a solid or solid and cystic carcinoma. This can occur without papillary projections, and it probably is what she had. Fibroma or cyst is a second bet.

I believe that the patient's death was due to liver failure on the basis of portal cirrhosis, possibly associated with a terminal cerebral thrombosis.

CLINICAL DIAGNOSES

Acute hepatic insufficiency.
Icterus.
Ascites.
Ovarian cyst.

DR. MOORE'S DIAGNOSES

Portal cirrhosis of liver.
Ascites.
Icterus.
Carcinoma of ovary.

ANATOMICAL DIAGNOSES

Toxic cirrhosis of liver, with superimposed acute hepatitis.
Thrombosis of portal and splenic veins, recent.
Splenomegaly.
Ascites, slight.
Icterus.
Cystoma of left ovary.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy showed a small liver that weighed only 950 gm. It was extremely cirrhotic, and the nodules of regenerated liver tissue varied from 0.3 to 1.0 cm. in diameter. This wide variation in the size of the nodules rules out the alcoholic type of portal cirrhosis and is characteristic of the healed atrophy or toxic type. What the toxic agent was remains unknown; but it is quite possible that in the antisiphilic treatment twelve years previously an arsenical was used that was the cause of the liver damage. Microscopically there was evidence of a superimposed acute hepatitis. Recent thrombi were present in the distal portion of the splenic vein and in the main portal vein. The spleen was about twice the normal size, and varices were present in the esophagus. At the time of the autopsy there was only about 100 cc. of bile-stained ascitic fluid.

The pelvic mass proved to be an innocuous simple ovarian cyst, measuring 12 cm. in diameter, on the left side. The brain showed diffuse nerve-cell degeneration of a terminal nature; there was no thrombosis. We found no evidence of syphilis anywhere.

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THE JOURNAL does not hold itself responsible for statements made by any contributor.

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MILITARY MEDICINE

Now that about 90 per cent of all residents, interns and medical students are either medical officers on inactive duty or enlisted men in the Army and Navy and are on an accelerated schedule, one cannot help but wonder how efficiently they are being taught regarding military medicine—that extremely specialized branch of medical practice in which all of them, sooner or later, will be involved.

The problems that confront the medical officer are, by and large, quite different from those that are ordinarily encountered in civilian practice. Of primary importance are the infections and parasitic diseases so prevalent in tropical and subtropical

regions but relatively unheard of in temperate zones. Preventive medicine and sanitation assume most significant roles, and then comes the fact that the methods of medical and surgical treatment in combat zones are, of necessity, entirely different from those in civilian communities. And added to all this are the constant advances that are being made as the result of directed research or of experience, which rarely, if ever, are brought to the attention of the future medical officer and of which even the majority of their instructors are ignorant.

Undoubtedly the Government, at the moment, has no intention of changing the curriculums of medical schools. On the other hand, it seems reasonable that schools and teaching hospitals could turn out men who would have a more thorough and exact knowledge of the military aspects of medicine than they do at present and that this could be done with slight inconvenience and with little change in the methods of teaching that are considered to be basic to all forms of medical practice.

Prior to the present war, only a few of the medical schools in this country had departments of tropical medicine. Within the past two years, the schools lacking such facilities have been given the opportunity of sending members of their teaching staffs to take the regular two-month course in tropical medicine at the Army Medical School in Washington, the expenses having been met by a philanthropic organization. In addition, many of the schools have increased their instruction in preventive medicine and sanitation. Thus, it seems likely that the majority of schools have voluntarily revised their curriculums to cover, more or less satisfactorily, certain subjects that are of utmost importance to the medical officer. On the other hand, it seems extremely unlikely that instruction in medicine, surgery and the various specialties in the schools and teaching hospitals is conducted with the proper emphasis on military needs, largely owing to ignorance of the instructors regarding military medicine in general and recent advances in particular.

There appear to be two ways in which this state of affairs can be improved. In the first place, members of the teaching staffs should be thoroughly cognizant of the military aspects of their specialty and should advise their students to refer frequently

to military manuals, such as those published by the War Department and those sponsored by the National Research Council. Secondly, pertinent directives and monthly bulletins issued by the Army and Navy to their medical officers on active duty should also be forwarded to the commissioned residents and interns, to the enlisted students and to all members of the faculties of medical schools. In this way, proper emphasis could be placed on military medicine, and the physicians concerned with teaching and the future medical officers would be apprised concerning recent accepted advances in the prevention, diagnosis and treatment of disease — an accomplishment that would also benefit civilian practice.

DENTAL NEEDS IN CHILDHOOD

THE report, entitled "The Dental Needs of Massachusetts Children of Today," appearing in the January 6 issue of the *Journal* cannot fail to awaken the thought of the medical profession and those concerned with public-health problems. It emphasizes the dental conditions in the Commonwealth, but dental caries is a national problem and exists in its rampant form wherever the pattern of our present civilization is found. This report is a dual challenge, both to dentists and to the medical profession.

The immediate challenge is to the dental profession to find new or more efficient technics and methods that will restore the ravages of dental caries in our youth before the age of induction into the armed forces. One might even suggest the slogan, "Treat the teeth and win the war." When one recalls the appalling number of draftees who are rejected because of dental conditions and the reported number of extractions and dental restorations that are made by dentists in the armed forces, it is not difficult to appreciate what a burden the dental problem has been on the war effort. This curtailment of efficiency is just as real as the hazards of production caused by strikes or by industrial or tropical diseases. The immediate problem is to organize some program that will ensure adequate dentistry for all boys from the ages of approximately twelve to eighteen. If this is accomplished,

it is not too fantastic to believe that the final date of the ending of the war might be changed. Although the dental profession has been stripped of its youth, it is not too much to believe that the remaining dentists, if organized, could care for this age group. It would necessitate new clinics, reorganization of technical procedures, proper compensation for services rendered, and possibly some neglect of the dental problems of those beyond the draft age. As an emergency measure, dental attention for this age group should be made compulsory, just as is vaccination against smallpox.

Prevention, the second challenge of this report, is the same as that met by groups of pioneers in other fields of medicine. It is the challenge that has practically controlled tuberculosis, syphilis and innumerable other diseases. A great industry is not satisfied to employ skilled engineers to care for its injured: it develops new machinery and new safeguards until the effects of accidents are reduced or eliminated.

Although the prevention of dental caries is not a war problem, it is one of the peace to come. As has been explained in the report of the committee, the etiology of dental caries is unknown. Students in this field believe that the best lead is through the study of nutrition. Whether it is due to some chemical disturbance in the organic structure of the tooth or to a defect in calcification is a problem yet to be solved. An example that has been utilized, namely that of a post placed in the ground with subsequent decay depending on its structure, is apt. Undoubtedly, the tooth structure is laid down in utero, and the first few weeks of life must have a profound effect on the formation of the tooth. Caries may well be due to faulty construction, and to determine when and why this occurs is a challenge to both the dental and the medical profession.

MEDICAL EPONYM

PONCET'S DISEASE

Antonin Poncet (1849-1913), professor of surgery von, published a paper, entitled "Faits de tuberculose simulant des lésions rhumatismales chroniques déformantes [Tuberculous lesions simulating the lesions of Chronic

"reforming Rheumatism]" in *La lancette française, gazette des hôpitaux civils et militaires* (70:1219, 1897), a portion of which is translated below:

On very careful examination it is seen that we are dealing with a deforming polyarthritides of tuberculous nature. It is a bacillary bony manifestation, usually in young subjects. It may be seen in older persons and then is difficult to distinguish from chronic deforming rheumatism.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

STATED MEETING OF THE COUNCIL

A stated meeting of the Council will be held in John Ware Hall, Boston Medical Library, 8 Fenway, on Wednesday, February 2, 1944, at 10.00 a.m.

Business:

1. Call to order at 10.00 a.m.
2. Presentation of record of meeting held October 6, 1943, as published in the *New England Journal of Medicine*, issue of November 25, 1943
3. Report of Auditing Committee and of Treasurer.
4. Reports of standing and special committees
5. Appointment of Delegates.

(a) To the House of Delegates, American Medical Association, for two years from June 1, 1944

(b) To the annual meetings of the five New England state medical societies in 1944.

(c) To the Annual Congress of the American Medical Association on Medical Education and Licensure at the Palmer House, Chicago, February 12 to 15, 1944.

6. Such other business as may lawfully come before this meeting.

MICHAEL A. TIGHE, M.D., Secretary

SECRETARY'S OFFICE

The following statement is submitted for publication in the *Journal* by order of the Executive Committee.

MICHAEL A. TIGHE, Secretary

* * *

The *Boston Herald*, issue of December 22, 1943, carried a news item to the effect that graduates of the Middlesex University School of Medicine, under a ruling issued from the office of the Surgeon General of the Army of the United States, would no longer be eligible for commissions in the Army Medical Corps.

In this item, C. Ruggles Smith, registrar and general counsel of this school, is quoted as suggesting that "the probable reason" for this action "was pressure from the American Medical Association."

A clipping of this item was sent to Dr. Olin West, secretary of the American Medical Association, whose reply is as follows:

December 27, 1943

Dr. Michael A. Tighe
Secretary, Massachusetts Medical Society
8 Fenway
Boston, Massachusetts

Dear Doctor Tighe:

Your letter of December 22 was delivered to this office this morning and I have read the newspaper clipping which was enclosed with your letter and have, of course, noted particularly the statement attributed to C. Ruggles Smith to the effect that the probable reason why recent graduates of this school are not being commissioned in the Army Medical Corps is that they were not members of the American Medical Association. I am sorry that I was not able to see your letter until this morning. I am sure that you are correct in your statement. I am sure that the American Medical Association is here and that it is the duty of the Surgeon General to see that the Army Medical Corps is composed of the best available medical personnel.

of Middlesex would not be commissioned as medical officers until a copy of the order is received. In so far as the Army Medical Corps is concerned, I sincerely hope that you have had a delightful Christmas Season and that the New Year will bring you a full measure of health and happiness. With all good wishes, I am

Very truly yours,

[Signed] Olin West

On December 23, 1943, the Massachusetts Medical Society received the first authoritative word on this subject when it received the following memorandum from the office of the Surgeon General.

WAR DEPARTMENT
Army Service Forces
Office of The Surgeon General
Washington 25

3 December 1943

MEMORANDUM FOR The Executive Officer,
Procurement & Assignment Service,
War Manpower Commission,
Room 609, 1778 Pennsylvania Avenue, N. W.,
Washington 25, D. C.

Subject: Discontinuance of Appointments in the Medical Corps Army of the United States, of Graduates of Middlesex University College of Medicine, Waltham, Massachusetts

1 It has been decided that effective this date, and including those cases now in process, that this office will no longer recommend the appointment of graduates of subject medical school as commissioned officers in the Medical Corps, Army of the United States

2 This memorandum is submitted for your information
For The Surgeon General

DURWARD G. HALL
Lt. Col., Medical Corps
Assistant

A TRUE COPY
(Signed) Durward G. Hall
DURWARD G. HALL
Lt. Col., Medical Corps
Assistant

COMMITTEE TO AID THE DISTRICT RATIONING OFFICER

The committee of the Massachusetts Medical Society appointed last June to aid the district rationing officer has met several times with the representative in charge of food rationing of the Office of Price Administration, and has considered carefully a considerable number of physicians' certificates of patient's necessity. The majority of these requests have been granted; with many, however, it has been necessary to cut the amounts of food requested to a maximum allowance that was determined after conference with a number of recognized authorities. In others, only the basic ration has been approved.

This maximum was established as 32 pounds of processed foods and 40 pounds of meats and fats for a two-month period, or roughly double the amounts received on basic rations. These maximum amounts have been exceeded only in special cases, and only after review by the medical committee.

It has become increasingly evident, however, that an alarmingly large number of requests are being made to the rationing boards, and are being granted if they call for amounts of rationed foods within the prescribed maximum limits. Although the exact number is undetermined, it probably runs well into the thousands, and is a just cause for concern, since, with a restricted available quantity of certain foods,

to military manuals, such as those published by the War Department and those sponsored by the National Research Council. Secondly, pertinent directives and monthly bulletins issued by the Army and Navy to their medical officers on active duty should also be forwarded to the commissioned residents and interns, to the enlisted students and to all members of the faculties of medical schools. In this way, proper emphasis could be placed on military medicine, and the physicians concerned with teaching and the future medical officers would be apprised concerning recent accepted advances in the prevention, diagnosis and treatment of disease—an accomplishment that would also benefit civilian practice.

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The immediate challenge is to the dental profession to find new or more efficient technics and methods that will restore the ravages of dental caries in our youth before the age of induction into the armed forces. One might even suggest the slogan, "Treat the teeth and win the war." When one recalls the appalling number of draftees who are rejected because of dental conditions and the reported number of extractions and dental restorations that are made by dentists in the armed forces, it is not difficult to appreciate what a burden the dental problem has been on the war effort. This curtailment of efficiency is just as real as the hazards of production caused by strikes or by industrial or tropical diseases. The immediate problem is to organize some program that will ensure adequate dentistry for all boys from the ages of approximately twelve to eighteen. If this could be accomplished,

it is not too fantastic to believe that the final date of the ending of the war might be changed. Although the dental profession has been stripped of its youth, it is not too much to believe that the remaining dentists, if organized, could care for this age group. It would necessitate new clinics, reorganization of technical procedures, proper compensation for services rendered, and possibly some neglect of the dental problems of those beyond the draft age. As an emergency measure, dental attention for this age group should be made compulsory, just as is vaccination against smallpox.

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Although the prevention of dental caries is not a war problem, it is one of the peace to come. As has been explained in the report of the committee, the etiology of dental caries is unknown. Students in this field believe that the best lead is through the study of nutrition. Whether it is due to some chemical disturbance in the organic structure of the tooth or to a defect in calcification is a problem yet to be solved. An example that has been utilized, namely that of a post placed in the ground with subsequent decay depending on its structure, is apt. Undoubtedly, the tooth structure is laid down in utero and the first few weeks of life must have a profound effect on the formation of the tooth. Caries may well be due to faulty construction, and to determine when and why this occurs is a challenge to both the dental and the medical profession.

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REFRIGERATION IN SURGERY OF THE EXTREMITIES

PAUL R. HINCHEY, M.D.*

SALEM, MASSACHUSETTS

THIS paper was originally completed as a case report of an unusually severe spreading infection of an arm, in which an unexpectedly favorable outcome followed the employment of a tourniquet and ice refrigeration prior to amputation. Refrigeration proved so gratifying, however, that the members of the Surgical Service at the Salem Hospital were encouraged to employ this form of therapy in several other suitable cases in which trial of this method seemed reasonable.

Broadly speaking, refrigeration therapy has been advocated for three types of surgical lesions of the extremities: arteriosclerosis with circulatory insufficiency, uncontrollable limb sepsis and severe trauma to the limbs with circulatory impairment. Our case total is small, but our experiences have been illuminating. Case reports illustrative of each of these three types of surgical lesions of the extremities are submitted in the order in which they were encountered.

LIMB SEPSIS

The first case was that of a desperately ill and toxic patient who had uncontrollable sepsis in a cold, pulseless arm, with beginning gangrene of the hand.

CASE 1. A 54-year-old leather worker was admitted to the Salem Hospital on December 17, 1942. Because of his toxic condition and language difficulty, no adequate history was obtained at entry, nor was it possible to obtain additional information later on. Apparently, a small break in the skin of the forearm had occurred at work 10 days prior to admission. There was also a questionable history of chrome dermatitis, with some pruritus and scratching. Five days prior to entry the forearm became swollen and the patient resorted to alcohol for relief. He continued at work until the day before entry. He had sought no medical advice prior to admission. On the night of entry the left hand had begun to turn black.

The patient was a strong, middle-aged laborer, rational but unco-operative. The temperature on admission was 102.6°F., the pulse 110, and the respirations 46. The white-cell count was 6100 and the hemoglobin 97 per cent. The blood pressure in the Out Patient Department at entry was 80/54. The left arm and hand were tremendously swollen and cool, and cyanotic to 7 cm. below the level of the shoulder joint. The coldness and cyanosis were progressively more marked as the hand was approached. The superficial layers of the skin over the lower forearm, wrist and hand had separated from the deeper layers, and there were multiple, thin-walled vesicles and bullae filled with blood-tinged watery fluid. The radial pulse was not felt, but a brachial pulse was

present. The hand was blue to black. The entire arm was extremely painful to touch. The appearance of the arm and the fact that it was a winter night suggested to the house officer an admission diagnosis of frostbite. Routine shock treatment was instituted, and 2 hours after entry a feeble radial pulse could be felt in the affected arm. On the night of entry, treatment consisted of continuous hot packs to the entire left arm and intravenous sodium sulfadiazine.

During the night of admission the systolic blood pressure ranged from 70 to 90. On the following morning the tem-



FIGURE 1. Photograph of the Left Lower Forearm and Wrist
Fifteen Hours After Admission.

perature was 103.8°F., the pulse 120, and the respirations 35. Twelve hours after entry, the patient was seen by four senior surgeons. He was extremely noisy and unco-operative and appeared very toxic. The face showed an ashen-gray hue, although the blood pressure was then 118/84. The entire left arm was cyanotic; most of the bullae had ruptured during

*Assistant in surgery, Harvard Medical School and Tufts College Medical School; junior surgeon, Salem Hospital.

the night (Fig. 1); no radial pulse could be felt despite the adequate blood pressure. The sulfadiazine level was 17.6 mg. per 100 cc. There had been no report on the blood culture or on the cultures of the fluid from the bullae. There was an even division of opinion among the consultants concerning the wisdom of immediate amputation, in contrast to a policy of delay with the hope of improvement in the general condition. Opinion was unanimous, however, that whatever course was followed, the patient was almost surely going to die. In this dilemma, application of a tourniquet and refrigeration seemed worthy of trial.

Accordingly, the entire left arm was packed in ice and a tight tourniquet was applied to the upper arm 7 cm. below the shoulder, using three turns of gum-rubber tubing. At that time it was planned to amputate the arm in a few hours,



FIGURE 2. Photograph of the Stump Prior to the Minor Operations.

but the patient, who was then partly delirious, refused permission. That afternoon the white-cell count was 5400.

On December 19, after 20 hours of tourniquet and refrigeration, there was an obvious dramatic change in the patient's condition and appearance. The temperature had dropped to 100.4°F., the pulse to 110, and the respirations to 20. He was quiet and oriented, had begun to take fluids by mouth, and appeared much less toxic. The skin was dry and warm, and the radial pulse in the opposite wrist improved in quality. By that time the blood culture had shown the presence of a hemolytic *Staphylococcus aureus*. Culture from the bleb fluid had shown the same organism and an anaerobic nonhemolytic streptococcus. Shaved ice had been used for refrigeration, but because an improvised apparatus was used, refrigeration up to the level of the tourniquet was incomplete. Nevertheless there was absolutely no sensation below the level of the tourniquet. Amputation was therefore performed 24 hours after the commencement of refrigeration and 36 hours after entry. Preoperative medication consisted of $\frac{1}{4}$ gr. of morphine sulfate and 1/150 gr. of scopolamine hydrobromide 1 hour before operation. An additional $\frac{1}{4}$ gr. of morphine sulfate was administered in the operating room, since the patient was wide awake. Nevertheless, he remained awake throughout the operation.

The operation was performed by Dr. D. S. Clark. The left forearm was prepared and draped. The tourniquet was not removed. A guillotine amputation was then done, with no other anesthesia than refrigeration and the tourniquet. No pus was encountered. The soft tissues were surprisingly firm, glistening and fairly normal in color. The transected muscle bundles had the appearance of well-refrigerated meat. Although the patient was wide awake and talking throughout

the operation he did not complain or show signs of discomfort at any time. No sutures were employed.

Thereafter the amputated arm was completely dissected by me. The tissues were edematous, but there was no evidence of any accumulation of pus. All the main arteries and veins were examined but no evidence of thrombosis was present.

The 7-cm. stump of the left arm was not refrigerated post-operatively, which was perhaps a mistake. The patient had a stormy convalescence for 10 days and was persistently disoriented, incontinent and cyanotic. The red-cell count dropped to 2,000,000. Extensive sloughing occurred in the narrow band of tissue below the level of the tourniquet, which had had to be left on for many hours. Surgeons with considerable experience with refrigeration have stated that amputation may be done at almost any level below the tourniquet in those limbs in which amputation is performed within four or five hours of the application of the tourniquet and the commencement of refrigeration. The patient was ambulant 1 week after the operation. Two subsequent minor operations were required to remove protruding bone and to approximate loosely the margins of the wound (Fig. 2).

The patient was discharged on March 1, 2½ months after entry, with the stump of the left upper arm well healed. He was last seen on May 1; he had gained 26 pounds in weight, felt well, and had no symptoms in the stump.

It seems worth while to present this report because the case was such a dramatic demonstration of the value of the application of a tourniquet and refrigeration. It is the conviction of all the senior surgeons that the patient would have died if he had been treated either by immediate surgery or by hopeful delay. The overwhelming toxicity due to sepsis, together with the clear evidence of marked circulatory deficiency in the limb, presumably due to vasospasm and edema, did not augur success for formerly accepted routines of treatment. Toxicity secondary to infection had produced a more or less intractable shock that could not be fully combated. The trauma of anesthesia and operation, added to the already existing shock, would almost certainly have been disastrous. Because of the impaired circulation to the limb, chemotherapy and the natural defenses of the circulation were destined to failure because the effective agent could not be brought to the site of the sepsis in therapeutic concentration. The initial treatment by hot pack was probably harmful, since the patient was in shock and the limb was not capable of a reactive hyperemia because of the vasospasm that was presumably present. Moreover, any increase in blood supply to the affected limb brought about by vasodilatation due to heat must have been more than offset by the accelerated metabolic demand for oxygen on the part of the anoxic tissues. But although an adequate blood supply and effective chemotherapy could not be provided at the local site of infection, it was obvious that toxins and bacteria were being liberated freely into the systemic circulation from the limb.

We asked ourselves whether the limb could be saved by refrigeration and systemic chemotherapy without the use of a tourniquet. Two considerations prevailed against this. In the first place, the cold, cyanotic, pulseless forearm and hand strongly suggested the onset of gangrene, so much so that it was unanimously thought that arterial thrombosis had

occurred because of intimal damage from pressure and sepsis together with peripheral circulatory failure. Moreover, it was apparent that the immediate physiologic amputation of the septic limb by a tightly applied tourniquet was imperative in order to put a quick stop to the continued entrance of bacteria and toxin into the general circulation. Refrigeration alone could not have produced any such an immediate result.

LIMB TRAUMA

Several recent cases of severe limb trauma treated at the Salem Hospital have suggested a number of questions concerning the value of refrigeration in such conditions. The following case is cited as an example.

CASE 2. A 9-year-old boy sustained a severe, crushing compound fracture of the right index, middle and ring fingers when a manhole cover fell on them. When he was first seen in the operating room 1½ hours after the accident, a complete compound fracture with fairly extensive laceration of the adjacent soft parts was found in all three fingers, just inside the proximal interphalangeal joints. Distal to this level of fracture the fingers were slightly cyanotic. It was recognized that there was serious circulatory impairment, but it was decided to be conservative. Accordingly the wounds were thoroughly irrigated with saline solution. The wound was dusted with sulfanilamide powder and skeletal traction fixation was secured by pins through the distal phalanx. Continuous refrigeration by shaved ice was employed with only a thin layer of gauze over the wound and with the fingers fixed in elastic-band traction on an arm board.

The arm was then elevated, and more or less continuous refrigeration was maintained for 12 days. No sign of sepsis appeared. During the 1st week the patient repeatedly stated that he was free of pain when his hand had been freshly iced, but that he had considerable discomfort after the ice had melted and until it was renewed. It was not known how long refrigeration should be maintained, but after 1 week the loosely covered hand was exposed to the air without refrigeration for varying periods. During this first week it was hoped that refrigeration was maintaining an equilibrium between the known impaired circulation and the local metabolic demand of the fingertips, reduced by the refrigeration. On several occasions, there appeared to be a suggestive, pinkish suffusion of the distal fingers. Certainly the flesh continued to look healthy and no cyanosis appeared. As the interval without refrigeration was increased, however, it quickly became apparent that we had succeeded only in refrigerating a dead tissue so that frank decomposition was forestalled. A few hours after refrigeration was withdrawn altogether, obvious gangrene was readily apparent. Amputation of the three fingers was finally necessitated at the same level at which it would have been done at entry. Convalescence was uneventful.*

The chief question that this experience brought to our minds was, For what length of time may one employ refrigeration with continued hope of improvement in such a borderline trauma with circulatory impairment?

Several recent papers assert the value of refrigeration in the management of limb trauma both in civil and in military practice. For the occasional case in which it is indicated, the procedure is simple and deserving of consideration. Even small hospitals can afford the equipment.

ARTERIOSCLEROSIS WITH GANGRENE

Recently, a splendid opportunity was afforded to make a comparison between refrigeration anesthesia

and one of the previously accepted forms of anesthesia, as employed in amputation of limbs for arteriosclerotic gangrene. Within one month an elderly patient was obliged to undergo amputation of both legs through the thigh because of arteriosclerotic gangrene associated with diabetes. For the first amputation, cyclopropane and nitrous oxide anesthesia was satisfactorily employed. More recently the second limb was removed under ice anesthesia together with the usual sedation.

CASE 3. A 70-year-old man with mild diabetes mellitus had narrowly escaped amputation of the left leg in the fall of 1942, when he was required to spend 3 months on the surgical ward and to undergo three minor local operations because of a septic blister on a toe. Optimism for such conservative surgical management seemed warranted by the presence of good pulsation of the dorsalis pedis artery and by the ready controlling of the mild diabetes. The patient, however, maintained no satisfactory regime of peripheral vascular hygiene, and in August, 1943, returned with frank gangrene of one of the toes of the right foot. There was no pulsation in this foot. Accordingly, on September 14 a routine midhigh amputation of the right leg was performed under cyclopropane and nitrous oxide anesthesia, which was quite satisfactory. Ordinarily spinal anesthesia would have been employed. Refrigeration anesthesia had been mentioned as a possibility. The operation required 35 minutes. The stump was dusted with sulfanilamide powder and closed without drainage. One hour later the patient complained of considerable pain in the leg. Three hours later, a preoperative blood pressure of 132/66 had dropped to 102/60. The patient was nauseated and showed signs of mild shock, for which elevation of the foot of the bed, warm blankets and Neo-Synephrine were employed.

The temperature first returned to normal on the 5th postoperative day. The patient did not get out of bed until the 7th day. He experienced the usual amount of postoperative pain. The stump dressing required several times in uneventful except for severe skin edges. The level of blood sugar was controlled with a little difficulty.

During the next 3 weeks, the tips of two toes on the left foot steadily became discolored. In addition, superficial sepsis at the site of a thickened callus at the base of the little toe progressed to involve the deeper tissues and eventuated into a chronic ulcer with an associated x-ray finding of complete destruction of the head of the 5th metatarsal bone. It was assumed that a Mönckeberg type of sclerosis of the small vessels existed, coincident with the diabetes, since satisfactory pulsation of the dorsalis pedis artery could be felt. During this period of waiting it was difficult to prevent those on the ward having care of the patient from employing heat from 100-watt bulbs directly over the weeping ulcer with the aim of drying up the lesion.

Finally, on October 18, the second limb was amputated through the thigh. Preliminary sedation was secured with Pantopon, scopolamine and 2 ounces of whisky. A 6-hour period of cracked-ice refrigeration was employed. A supracondylar amputation was done, since it was thought that less shock would attend tissue trauma through the tendons at this level than through the muscle masses at midhigh.* Thirty-five minutes was consumed in performing the operation. The patient grimaced when the sciatic nerve was crushed and cut across. It was thereafter injected with 3 cc. of absolute alcohol. Otherwise, he felt no pain. No chemotherapy was employed. A single layer of sutures approximated the muscle group.

The patient sat up in bed and ate lunch 1 hour after the completion of operation. He sat up in a chair that afternoon and every day thereafter. He did not go into shock, as was the case after the first operation. The postoperative pain was about the same as after the first operation. The temperature became normal on the 4th postoperative day. The

*Amputations below the knee in occlusive arterial disease have recently been proposed by Rickel and Ghormley, in cases in which adequate circulation at this level justifies the procedure. They argue that the chance for a later satisfactory prosthesis is appreciably greater than if the usual midhigh amputation is done.

dressings showed no staining, in contrast to the first amputation. Nausea and vomiting, however, were a little more pronounced after this operation than after the first, possibly because of the release of the tourniquet just prior to amputation. (It has been argued that premature release of a tourniquet may be productive of shock, due to absorption of histotoxins, in patients in whom widespread sepsis or severe tissue trauma exists.) The diabetes showed about the same reaction to this second amputation as to the first. Wound healing progressed uneventfully.

This case demonstrated that it is possible to secure satisfactory anesthesia by ice refrigeration. The mechanics of such anesthesia proved to be more of a chore than is the case with the usual low-spinal anesthesia. It is the impression of several surgical observers that the postoperative convalescence after the second amputation using refrigeration anesthesia was definitely more satisfactory than that after the first operation but the percentage of improvement was perhaps a small return for the additional work required. Hence, we are not yet willing to resort to this cumbersome procedure for anesthesia as a routine for all amputations in arteriosclerotic gangrene. We have been convinced that satisfactory anesthesia can be secured by the method, and that there are occasional cases in which its employment provides the most satisfactory solution to the problems of securing anesthesia and minimizing systemic reaction to surgery of the extremities.

DISCUSSION

Clinical use of the principle of refrigeration of limbs is concerned almost exclusively with those limbs in which efficient circulation does not exist. Following the pioneer lead of Fay,² Allen³⁻⁷ elaborated on the principle of refrigeration. Thereafter Smith,⁸ McCravey,⁹ and Whittemore, Lisa and Sauer,¹⁰ made further contributions. From Allen's experimental observations on tissue asphyxia in relation to the temperature of the environment, he was prompted to study the survival time of tissues with inadequate blood supply when exposed to heat and to cold. Heat accelerated necrosis, whereas cold markedly prolonged the survival time of anemic tissues. Oxygen consumption of the tissues is reduced progressively for each degree Centigrade by which tissue temperature is lowered. Allen made the first clinical application of laboratory observation in cases of arteriosclerotic gangrene of the leg. Subsequently, the value of refrigeration in arteriosclerotic gangrene and in limb sepsis and trauma has been repeatedly confirmed by Allen and all other observers¹¹⁻¹⁷ who have made the clinical trial. It is worthy of repeated emphasis that the essential feature in all these cases has been a deficient circulation to the limb. Very few observers have claimed any merit for refrigeration when normal circulation is present. Conditions of trauma or of sepsis can be better handled by the tissues with the aid of their normal physiologic inflammatory reaction than by suppression of this reaction by refrigeration. The assets of this normal inflammatory response are

increased exudate, increased absorption and increased local heating of tissues with accelerated tissue metabolism. At the same time there is a greatly increased tissue demand for oxygen, out of proportion to the increased local blood flow. In a limb with deficient circulation, a disparity may exist between the supply and the demand for oxygen on the part of the tissue cells; hence, necrosis of tissue may occur if an inflammatory response is provoked. The refrigeration of such tissues is beneficial because it retards the oxygen demand of the tissues to a level commensurate with the available oxygen brought to the limb by the deficient circulation. This metabolic adaptation is apparently the principal benefit resulting from refrigeration, but there are a number of other advantages emphasized by Allen and confirmed by almost all investigators, as follows. First, there is efficient anesthesia, secured by the action of refrigeration on nerve trunks and also by what Allen terms "anesthesia of protoplasm." Second, anesthesia of protoplasm, in contrast to nerve anesthesia, is said to be a factor in preventing shock; shock is also lessened by the diminished tissue necrosis, diminished bacterial growth and the diminished absorption from the local site because of the vasoconstriction brought about by refrigeration. Third, local infection and edema are inhibited. This is in line with the familiar preservation of tissues in an icebox for days or weeks. Fourth, desired drainage from an amputation stump for the first few postoperative days is facilitated, because cooling of the tissues prevents the usual agglutination of the wound edges. Thus, postoperative sepsis in the stump is minimized. Lastly, the tendency to thrombosis and intimal damage of blood vessels is greatly lessened. Venous thrombosis in amputated stumps has recently been emphasized by Veal¹⁸ as a frequent cause of postoperative fatality, owing to subsequent embolism.

It has been demonstrated by experimental and clinical experience that all the above benefits may be conferred on patients, in varying degrees, by the process of refrigeration alone, except that anesthesia is not so complete. In clinical practice, however, refrigeration and a tightly applied tourniquet are usually employed, except in occasional cases where a reasonable hope of survival of the affected limb exists. Even in this situation a tourniquet may be applied to the refrigerated limb for some hours and perhaps several days, without compelling amputation because of necrosis distal to the tourniquet. It is necessary, therefore, to give some consideration to the role that the tourniquet plays in the improvement of the patient's condition. First, toxic absorption from a hopelessly traumatized limb or a septic limb is controlled. The tourniquet also plays a significant role in the control of shock resulting from a septic or traumatized limb, as shown in recent studies by Duncan and Blalock.¹⁹ Lastly, the boon of adequate anesthesia by refrigeration is often lost

unless a tightly applied tourniquet has completely shut off available circulation, since successful chilling of tissues is directly proportioned to the degree of reduced blood flow. In our reported case of sepsis there can be no question that the immediate physiologic amputation of the septic limb by a tight tourniquet was highly useful in the control of toxic and septic absorption.

Technic

The essential points of technic with tourniquet and refrigeration have been fairly well established. The refrigeration of limbs has been secured by shaved ice, ice water, or electric or gas refrigeration units.



FIGURE 3. Photograph of the Refrigeration Box.

A common device is to employ a rectangular box into which the affected limb can be placed, and then surrounded by ice. We secured a refrigeration box modeled after the one proposed by Gordon²⁰ (Fig. 3). Preliminary refrigeration by ice bags at the level of application of the tourniquet will suffice after a few minutes to permit a tight application of narrow gum-rubber tubing applied several times around the limb. Allen²¹ states that a narrow tourniquet is more satisfactory than a broad one. Incomplete anesthesia may result if the tourniquet is not tightly applied, since it will be more difficult to refrigerate the tissue. The limb must be refrigerated to the level of the tourniquet. The desired level of temperature is about 5°C. which will effectively chill the tissues without actually freezing them. Lake²² has found that at a temperature of -6°C. all metabolic processes are inhibited. Therefore the thermal level of refrig-

eration is important, since actual freezing causes irreparable tissue damage, with the loss of large amounts of protein fluid at the site.²³ If saving the refrigerated limb is contemplated, actual freezing must be guarded against by skin-temperature readings. The temperature of the limb immersed in ice may be recorded by thermostat or by simple thermometers held against it. In a patient in good general condition, amputation through the lower thigh may be done with complete refrigeration anesthesia after two and a half hours. Amputation just below the knee requires about two hours for satisfactory anesthesia. A progressively shorter time is required as one approaches the foot because of the diminished mass of the limb and the increased ease of thorough chilling. If the amputation is done within six hours of the application of the tourniquet, almost any level of amputation distal to the tourniquet may be selected with confidence that healing will occur. If the tourniquet is to be left on longer than six hours, it should not be removed prior to operation, since overwhelming shock or generalized sepsis may result from its premature release.⁹ When a tourniquet has been left on for longer than six hours, amputation must be done at or within a few inches of the level of the tourniquet. Refrigeration greatly prolongs the safe period during which a tight tourniquet may be applied. Hence it is suggested that refrigeration is adaptable to wartime injuries of the extremities because it lengthens the safe period of tourniquet application and provides complete anesthesia for later surgery.²⁴ In poor risk patients, the tourniquet may be left on for as long as two days while the general condition is being improved. Preliminary sedation may be administered prior to the operation, but oftentimes it is unnecessary. Whiskey is a good sedative for elderly arteriosclerotic patients.

It is a common experience to obtain complete anesthesia by refrigeration and tourniquet only, without the use of any other agents. The two procedures that test the adequacy of refrigeration anesthesia are the cutting of the sciatic nerve at mid thigh and the sawing of the femur. Following operation, it has been recommended by Allen¹⁰ that refrigeration of the stump be maintained by means of ice bags against a thin dressing, gradually reducing the refrigeration over a period of several days. A number of writers^{13, 14} have commented on the fact that elderly, poor-risk patients are able to return to their rooms, sit up out of bed on the day of operation, and eat their meals, in contrast to the usual weakness and depression of similar patients who have received spinal anesthesia for leg amputation. Wound healing is steady, although slower, with refrigeration. Stump sepsis is said to be lessened, presumably on the basis that postoperative wound drainage is usually more profuse, since the refrigeration inhibits the normal agglutination of the wound margins. Haley¹² comments that a rise in

postoperative temperature after an amputation done under refrigeration anesthesia is not so prolonged as after amputation under spinal anesthesia.

Indications for Use

Arteriosclerotic gangrene. This has been the most frequent lesion in which refrigeration anesthesia has been used. Two distinct types of cases have been treated. When amputation is inevitable in nontoxic patients in poor general condition, the application of a tourniquet and refrigeration have provided a quick, satisfactory anesthesia within several hours, accompanied by minimal reaction to the operative procedure. On the other hand, if spreading sepsis predominates in the arteriosclerotic limb, permanent and continuous refrigeration may be employed for a period of days while the general condition is being improved.

Sepsis. Cases similar to the one reported in which a previously normal limb is the site of uncontrollable sepsis have been infrequently reported. Refrigeration appears to be efficacious in forestalling the spread of sepsis.

Military wounds. Allen and Crossman²¹ have stated that tourniquet refrigeration provides freedom from pain, hemorrhage, shock and infection and allows either an immediate operation without other anesthesia or long deferment of operation without harm, if such a step is indicated. They emphasize that the safe period for the application of the tourniquet is greatly lengthened by refrigeration. They point out that refrigeration is usually available on naval vessels, and that a 200-pound apparatus that can be operated by the motor of a truck will refrigerate four to six limbs simultaneously. Bowers²⁵ has related favorable experiences in the treatment of cases of vascular trauma of the extremities encountered in a station hospital (Camp Gruber, Oklahoma). He found the fluorescein circulation-time test to be of value in the estimation of circulatory adequacy in refrigerated limbs. Criteria of failure of compensatory collateral circulation are listed.

Miscellaneous. Holman²⁶ suggests that in cases of limb trauma accompanied by concussion of the main artery with subsequent segmental arterial spasm, initial refrigeration enhances the survival of such a limb. In the immersion-foot syndrome, the principle of refrigeration has been employed to provide therapeutic cooling of hyperemic painful feet during the early stages.^{27, 28} Such cooling without actual refrigeration is also useful in cases of frostbite, and we have recently treated a patient with moderately severe frostbite in this manner. Mock²⁹ has successfully employed refrigeration anesthesia for the taking of skin grafts from the thigh.

SUMMARY

The principle of refrigeration has been established as a useful and at times lifesaving procedure in the

management of arteriosclerotic limbs with gangrene. A case is cited in which refrigeration anesthesia is favorably compared with general anesthesia.

Refrigeration may also be employed successfully in certain cases of trauma or sepsis of the limbs. A case is reported in which it is suggested that life was saved by the employment of refrigeration and a tourniquet.

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AN ERUPTIVE FEVER INVOLVING THE MOUTH AND EYES (STEVENS-JOHNSON'S DISEASE)*

Report of a Case

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IN 1922, "a new eruptive fever associated with stomatitis and ophthalmia" was reported by Stevens and Johnson.¹ A score of similar cases have since been added to the literature, all with unwieldy names, such as "erythema multiforme bullosum with involvement of the mucous membranes of the eyes and mouth."² No suitable name has been proposed for this disease, which appears, as cases accumulate, to merit recognition as a discrete syndrome. It is a bizarre disease of dramatic onset and course, and there are so many features common to each reported case that it seems justifiable to separate them from erythema multiforme and other established entities of this order.

This disease is one of acute, sometimes fulminating, systemic reaction with fever and prostration, erythematous generalized skin rash and severe stomatitis, followed by sloughing. With occasional exceptions³ the conjunctivas are involved. The usual period until resolution of the skin lesions is about three weeks.² All laboratory studies have revealed normal or variable findings, including blood-cell counts, blood cultures,⁴ smears and cultures of lesions,^{4, 5} a skin biopsy⁶ and studies of the chemical constituents of the blood.⁴ The suggestion that Vincent's stomatitis may be associated etiologically with the disease⁶ has not been confirmed.²

The following case is reported because it illustrates clearly the most constant clinical findings of this disease.

CASE REPORT

J. M., a 22-year-old, unmarried man of Italian parentage, was admitted to St. Luke's Hospital on February 5, 1943, complaining of blisters in his mouth that had first appeared 2 days before admission, and had progressed since that time. He had had no previous illnesses, and had enjoyed excellent health except for a moderate tendency to upper respiratory infections. He had had a cough and mild malaise in the 2 weeks previous to admission. He had recently used an elixir of terpene hydrate and codeine, and had taken a few tablets compounded of aspirin, acetphenetidin and caffeine, but no other drugs. He had also gargled with a strong solution of

sodium chloride. The present illness began 3 days before admission with a swelling between the upper lip and gum, where the patient noticed burning on taking food. Later blisters began to appear on the buccal mucous membrane.

Physical examination showed a well-developed and well-nourished, swarthy-skinned man who appeared comfortable. The temperature was 101° F., the pulse 120, and the blood pressure 112/76. The conjunctivas were diffusely inflamed. The buccal mucous membrane, gums, palate and uvula were covered with many tight vesicles the size, shape and color of medium-sized pearls. There was also a small amount of red inflammatory reaction and sticky exudate about the urethral meatus. The rest of the examination was negative.

Routine laboratory studies showed a normal chest film and electrocardiogram. The urea nitrogen was normal, and a blood serologic test for syphilis was negative. The red-cell sedimentation rate was slightly elevated (33 mm. per hour), which may have been caused by the respiratory infection.

The patient remained in the hospital for 17 days. During the first 2¹/₂ course, The ran a hectic gressed with striking speed during this time. All the pearl-like vesicles in the mouth quickly ruptured, leaving a loose, dirty, whitish slough. By the 3rd day there was a massive slough several millimeters deep affecting the entire mucous membrane of the mouth and sparing only the tongue, which was heavily coated. This process extended out over the lips almost to the vermillion border. The surface thus uncovered was raw and angry red, and bled easily when touched. The nasal mucous membrane sloughed in the same, though a less dramatic, manner. Large blebs appeared on the glans penis and one on the corona, both also with superficial sloughs. Both conjunctivas were markedly inflamed, but no vesicles formed about the eyes. A sticky, semipurulent exudate flowed continually from the eyes. On the arms and legs a few punctate red areas began to appear and expanded, and in the center of each a tight little vesicle appeared. These vesicles ripened into thin-walled bullas, and eventually ruptured. They were scattered over all four extremities, but spared the trunk and face.

On the 5th day the temperature fell and the patient began to improve. He continued to recover gradually, although the sloughs in the mouth and on the penis were not complete before the 3rd week. Photographs taken on the day before discharge (the 16th day) show the residuums on the lips (Fig. 1), buccal mucous membrane (Fig. 2), legs (Fig. 3) and penis (Fig. 4).

The blood on admission showed normal red elements and a white-cell count of 12,000 with 80% polymorphonucle.

latter figure and the white-cell count as a whole gradually fell to normal. Blood cultures and aspiration cultures of the bullas were sterile. A conjunctival culture yielded *Staphylococcus aureus*. Smears of the bullas were negative both for *Staphylococcus aureus* and for *Streptococcus* and for organisms. Common heavy metals. 24-hour urine specimens.

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The patient had had a mercury-amalgam tooth filling 1½ months previously, but no other significant metal or drug

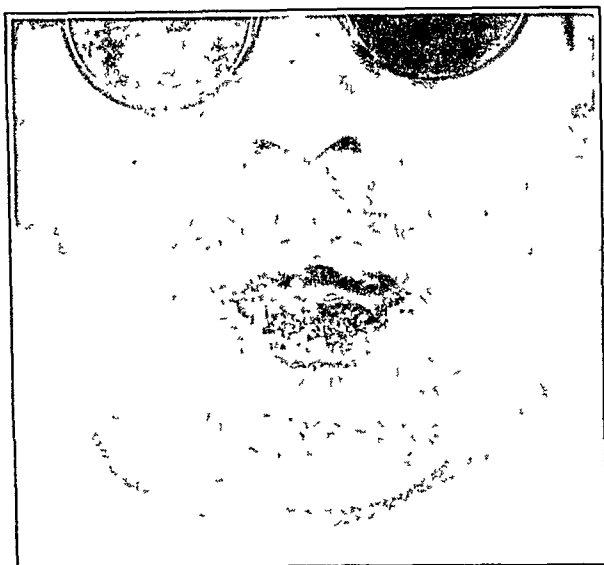


FIGURE 1. *Late Lesions on the Lips.*

history could be elicited from either the patient or his dentist.

The therapeutic measures employed included sulfadiazine in full doses for 5 days, the forcing of fluids, colonic irrigations, calcium gluconate intravenously and numerous salves,



FIGURE 2. *Re-epithelialization of the Lesions of the Buccal Mucous Membrane.*

washes and other local applications to the mouth, penis and eyes.

At the end of 17 days the skin lesions had crusted and mostly fallen away with healing beneath, and before the end of the 4th week the scars were barely visible.

DISCUSSION

Stevens and Johnson¹ outlined most of the features of this disease with their "two cases of an extraordinary, generalized, eruption with continued fever, inflamed buccal mucosa and severe pur-

ulent conjunctivitis." Although the skin lesions of these cases were not vesicular or bullous as in the present case and numerous others,^{2-4, 6} the appearance of the buccal mucosa was almost identical, with the formation of tight vesicles that ruptured and progressed rapidly to a membranous slough. The exact appearance of the skin lesions, in fact, appears to vary somewhat in different cases, and Stevens and Johnson even repudiated as inadequate the diagnosis



FIGURE 3. *Late Lesions on the Right Leg.*

of erythema multiforme. The reaction of the buccal mucous membrane is more characteristic. Ginandes's⁴ description of the mouth lesions corresponds exactly with the picture presented on about the fourth hospital day, in the case above: "The entire buccal mucosa was red, ulcerated in spots and covered with a whitish pseudomembrane which was friable and appeared like ruptured bullas. These lesions varied in size and were surrounded by a zone of marked congestion. The hard and soft palates were diffusely mottled and similarly covered with greyish-white patches." In almost every case in the literature,^{2, 3, 4-6} the conjunctivas were inflamed and produced a sticky, purulent exudate, as in the case

herein described. The most serious sequela reported was panophthalmitis and total destruction of the eyes, in one of Stevens and Johnson's patients. This complication is said to have occurred in several other cases.² There is only one previous report of



FIGURE 4. Late Lesions on the Glans Penis and Corona.

penile lesions,⁶ although Ageloff² described massive vaginal involvement in a four-year-old girl.

The disease is definitely in the pediatric sphere, rare exceptions being the case reported and that of Levy.³ The age limits are said to be twenty-two months and sixteen years.² With rare exceptions,² the condition is found only in male children.

SUMMARY AND CONCLUSIONS

A case is presented that is typical of a growing number of cases being reported in the literature, known by such names as "erythema multiforme bullosum with involvement of the mucous membranes." This is one of a number of obviously unsatisfactory names, since it is unwieldy, the disease is not typical of erythema multiforme, and it is the enanthem rather than the exanthem that seems to be its constant feature. The condition begins with a violent constitutional reaction with fever of abrupt onset and with marked prostration. A vesicular stomatitis develops, the vesicles rapidly burst, and a membranous slough forms that leaves a raw buccal and palatal surface behind it. There is almost invariably a diffuse conjunctivitis with a sticky, purulent exudate. This last feature may predispose to the most serious complication of the disease — panophthalmitis and permanent destruction of the eyeballs and therefore constitutes, at the present stage of knowledge, the major point of therapeutic or prophylactic departure.

Nothing is known of the fundamental nature of the disease or of its etiology. Neither drugs nor Vincent's organisms have been implicated, and no other factor of importance has even been suggested. The greatest progress to date is the recognition of the syndrome in its own right, by virtue of several isolated reports describing a closely similar picture.

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PULMONARY ACTINOMYCOSIS

Treatment with Sulfonamides

NAHUM R. PILLSBURY, M.D.,* AND JOSEPH D. WASSERSUG, M.D.†

SOUTH BRAINTREE, MASSACHUSETTS

PULMONARY actinomycosis is uncommon. At the Johns Hopkins Hospital only one case was found in 12,000 consecutive autopsies.¹ The prognosis is poor and most cases end fatally.¹⁻⁵ The treatment of actinomycosis has in general been unsatisfactory. Iodine is the time-honored weapon against this fungus infection, but thymol, roentgen rays, a variety of vaccines and recently sulfonamides have been used. Masson⁶ reported clinical cures in 2 cases of abdominal actinomycosis by roentgen-ray therapy, but, as a rule, roentgen-ray treatments are only partially effective or totally ineffective. Neuber⁷ advocated "specific" vaccines, convalescent serums and autohemotherapy, but his practically 100 per cent cures still lack confirmation.

Several recent reports have stressed the effectiveness of the sulfonamides even when other treatments were at best of only slight benefit. In a case of abdominal actinomycosis, Walker⁸ reported healing three weeks after sulfanilamide was begun and after iodides had apparently proved of no value. Miller and Fell⁹ tried thymol, potassium iodide and roentgen rays, but their patient became progressively worse. Sulfanilamide therapy was instituted and improvement was noted in one week.

Sulfanilamide has also been used in pulmonary actinomycosis. Morton⁴ reviewed a case that failed to improve with 400 gr. of potassium iodide daily and roentgen-ray treatments. He stated that sulfanilamide and promin made a definite improvement in the general condition, whereas potassium iodide, even in massive doses, was of only moderate value. Of several different treatments used by Dobson, Holman and Cutting,¹⁰ sulfanilamide seemed to be the most effective therapeutic agent. Wilkinson¹¹ also obtained good results with sulfanilamide and recommended that it be given for several weeks, if necessary. Temporary benefit was obtained by Schneider and Finucane,⁵ but their patient died of complications resulting from pneumothorax and not from actinomycosis.

Sulfapyridine has been employed effectively in both abdominal and pulmonary actinomycosis. Ogilvie¹² treated a young girl with abdominal actinomycosis by massive doses of potassium iodide, but she failed to improve. Sulfapyridine was then given and the response was so favorable that the drug was discontinued in thirteen days. Mitchell¹³ tried tincture of iodine and oral actinomycotic vac-

cine, with no success. Sulfapyridine brought about prompt healing of sinuses and apparent clinical cure.

The following case of pulmonary actinomycosis is reported not only because of the rarity and seriousness of this disease, but more especially because sulfonamides appeared to be of considerable therapeutic value.

CASE REPORT

T. M. C. a 29-year-old housewife, was first admitted on September 4, 1940, after a chest roentgenogram, taken because of a tuberculous husband, had revealed tuberculosis. The past history disclosed incision of the cervical lymph nodes in 1930 and pleurisy 4 months before admission.

Physical examination was essentially negative except for a scar on the right side of the neck and fine rales in the left axilla. A roentgenogram showed areas of increased density in both lungs at the level of the first anterior intercostal space. The urine was negative. Blood examination revealed slight anemia. The sedimentation rate was increased. A Mantoux test was positive. The sputum was negative for tubercle bacilli, but a gastric specimen was positive by guinea-pig inoculation. On November 11, the patient left the hospital against advice.

On April 1, 1942, the patient was readmitted because of pain and swelling in the left chest wall, fever and marked loss of weight. One and a half months before re-entry she had gone to another hospital because of a pain in the left chest of 1 month's duration. While there, the left pleural cavity was incised and 2 cc. of thick pus was obtained. On re-entry, the patient appeared extremely ill, thin and pale. A 2-cm. scar was present just below the inferior angle of the left scapula, and a fluctuant hot swelling extended from this point downward to the tenth rib. A roentgenogram of the chest showed a density consistent with fluid in the left intrapleural space and fibrosis in the left first intercostal space. The temperature was 101° F., the pulse 140, and the respirations 28. The urine was negative. The red-cell count was 3,900,000 the hemoglobin 76 per cent, and the white-cell count 10,500. A blood Hinton test was negative. The sputum and gastric contents were negative for tubercle bacilli by concentration and guinea-pig inoculation.

The day following admission, 2cc. of thick pus was obtained by aspiration of the chest abscess. This pus proved negative for tubercle bacilli by smear, culture and guinea-pig inoculation, but a smear and culture showed *Actinomyces hominis*. Aspiration was repeated on April 10, and 150 cc. of pus containing numerous sulfur granules was obtained. Within the next 2 weeks four sinuses developed at the site of the abscess. In May the patient developed a productive cough, and sulfur granules were found in the sputum. Potassium iodide was begun on May 1 and the dosage was gradually increased to 3 gm. daily.

Abscesses and sinuses then began to appear on the left anterior chest wall and the general condition became worse. On May 22, the patient's name was placed on the danger list. The red-cell count was 3,500,000, the hemoglobin 66 per cent, and the white-cell count 22,000, with 86 per cent neutrophils, 7 per cent lymphocytes, 4 per cent monocytes and 3 per cent eosinophils. Sulfanilamide (6 gm.) was given that day. The next day the dose was reduced to 4 gm. From May 24 to June 12 the patient received 3 gm. daily. Abscesses were aspirated on two additional occasions in May and June. Actinomycotic sulfur granules were still present. The patient improved clinically, however, and on June 6 potassium iodide was discontinued. On June 25, her name was removed from the danger list.

The patient's condition during July appeared stationary. Six chest sinuses were still draining. Sulfanilamide (4 gm.

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daily) was resumed on July 23 and continued until August 15, when sulfathiazole was substituted. This was not tolerated and was discontinued after 2 days. Potassium iodide (2 gm. daily) had been resumed on July 23, and the dosage was gradually increased so that by August 29 the patient was receiving 9.3 gm. daily. Iodides were discontinued on September 13 because of a rash on the chin, but were resumed in gradually increasing doses so that by October 1 10.6 gm. daily was being given. The iodides were continued during the remainder of the hospitalization.

The temperature and pulse showed small but almost daily elevations during the summer, and soreness in the left chest was again noted. Sulfadiazine (4 gm. daily) was begun on September 12. Drainage from the sinuses decreased, and

tuberculosis merely because the common pyogenic organisms cannot be found in the pus. Even in a case such as the present one, where there was a proved antecedent history of tuberculosis, a search should be made for fungi as well as tubercle bacilli and pyogenic bacteria.

Since 1938 at least 5 cases of pulmonary actinomycosis have been reported in which arrest or cure of the disease has been attributed largely, if not wholly, to sulfonamide therapy. The impression

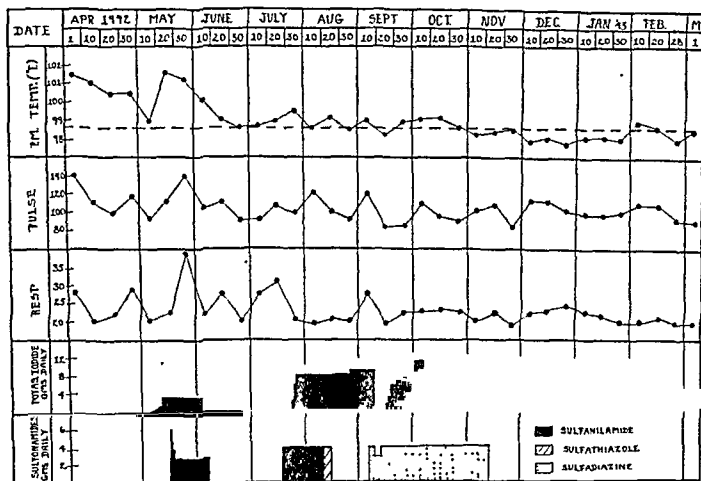


FIGURE 1. General Trends of Temperature, Pulse and Respirations, with Accompanying Therapy.

improvement in the condition was so remarkable that sulfadiazine was discontinued on November 16.

In addition, on November 16, the patient received ferrous sulfate for her anemia and vitamins to supplement the diet. Blood-cell counts and urine examinations were made almost daily. The patient continued to improve and the chest soreness disappeared entirely. On March 1, 1943, she was discharged.

Figure 1 shows the general trends of the temperature, pulse and respirations during the entire period of illness, as well as the therapy.

At a follow-up examination on January 8, 1944, the patient felt well and had gained fourteen pounds. She denied cough, expectoration or pain. The sinuses had been dry for more than 6 months, and she had been working for 4 months. She was continuing to take 5.3 gm. of potassium iodide daily. A chest roentgenogram was essentially negative except for an area of density in the left base that was apparently due to thickened pleura.

DISCUSSION

Because of its rarity, the diagnosis of pulmonary actinomycosis is frequently missed. Sulfur granules are not always present in the sputum or in the pleural exudate, and even when they are they may not be evident on casual inspection. One must not assume that a chest abscess or empyema is due to

gained from a study of the case reported in this article is that improvement and recovery were definitely enhanced, if not actually brought about, by the use of sulfonamides. Since iodides were also given almost throughout the hospital stay, it is impossible to offer incontestable proof that the sulfonamides alone were responsible for the patient's recovery.

Because iodides in massive doses have been so long regarded as an aid in the treatment of actinomycosis, there is a natural reluctance to abandon them entirely for newer methods of treatment. If iodides are of value at all, their worth is augmented by sulfonamides. It appears likely, however, that sulfonamides are more effective than iodides and may soon replace them entirely in the therapy of actinomycosis.

An interesting side light on this case is that the patient, who had a proved history of tuberculosis, received more than 1800 gm. of potassium iodide in a period of seven months without any evidence of reactivation of the tuberculosis. In an arrested case of tuberculosis iodine should apparently not

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and hernia in scar was markedly less in the transverse group. These writers stress a great diminution in postoperative pain and discomfort. They state that Baudelocque⁴ advocated the transverse approach nearly one hundred and twenty-five years ago, and used it in cesarean section.

Since Pfannenstiel,⁵ in 1900, advocated a transverse approach to pelvic surgery, there have been numerous advocates of some modification of the method to the abdominal cavity in general. Singleton and Blocker⁶ made an exhaustive study of the anatomical approaches to abdominal viscera in relation to wound disruption. Although their incisions were not quite what is interpreted as transverse, they were intended to accomplish much the same purpose. Gurd⁷ has strongly advocated the transverse approach to the exclusion of all others. Farr⁸ has also contributed much to the subject.

The use of transverse incisions has been adopted in some clinics with considerable regularity, whereas in others it has been used sporadically. At the Massachusetts General Hospital it is believed that many lesions are more easily handled through this approach. There are many patients whose wide-flaring costal angle make a transverse incision desirable for lesions of the upper abdomen. In the patient with a narrow, elongated costal angle, better exposure to the upper regions of the abdomen can be obtained through a long paramedian incision. With the use of nonabsorbable suture material, careful avoidance of nerve damage, absence of drainage through the wound, proper closure and the elimination of postoperative distention and vomiting, there will be less choice between the two methods.

Intestinal Trauma

Intestinal trauma during laparotomy has been properly condemned by Martland.⁹ He found the imprints of forceps, used by the surgeon in returning the small intestine to the abdominal cavity, at autopsy in 2 cases. In one case, 1500 cc. of blood that had come from such injuries was found in the lumen of the bowel. In another, he found more than forty of these imprints on the small bowel. In both cases, the surgeon had used a form of intestinal forceps devised for other purposes. They were of the kind that take a wide bite in the intestinal wall, producing a crushing defect that destroys the mucosa and submucosa. Such instruments are of little value for any purpose in intestinal surgery, and should never be used to grasp a segment of bowel that is not to be resected. Since instruments of this type are available, the only safe dictum seems to be to use no instrument in handling the intestine either during exploration or in returning the bowel to its natural position. Better anesthesia and the proper use of gloved hand and abdominal retractors will eliminate the need of a more traumatizing technic.

Drainage of Peritoneal Cavity

Drainage of the peritoneal cavity has been criticized by Cutler.¹⁰ It is amazing that there is still fixed in the minds of many surgeons the belief that the peritoneal cavity can be drained. When there is widespread abnormal fluid within the abdomen, it must be realized that adequate drainage to the outside is almost impossible to establish. The temptation is too great to resist, however, and is apt to lead to the establishment of some variety of foreign body from the depth of the cavity to the periphery. That a certain amount of the fluid contents surrounding the intestines can be led off for a short period of time is acknowledged. That these so-called "drains" not only fail to reduce the incidence of residual abscess but are an extra hazard, in that they form the basis of point obstruction to the bowel by adhesive bands, is obvious to all who have followed the course of these cases.

One does better to remove contaminated or irritating fluids, such as duodenal or gastric contents from acute perforation and bile, when such has escaped widely, by means of the suction tip. Closing the source of the leak is important if this has not already been spontaneously accomplished. In diffuse peritonitis of the inflammatory type seen in perforated appendicitis, one can seldom aid in the recovery by the establishment of drains to the gutters and the pelvis, as is so often practiced. Much can be accomplished by the drainage of a localized abscess or an area where leakage may take place. Care must be used to avoid contact with a suture line or it will leak in a disconcerting manner; also, material used for drainage must not come in contact with the small bowel.

Care should be used to place drains from the biliary system away from the main wound if possible. Needless wound infection, dehiscence and hernia in the scar can thus be avoided.¹¹ The suction method of Chaffin¹² has been used at the Massachusetts General Hospital to hasten the resolution of an abscess cavity. Our experience with this method in bile peritonitis has met with less success. It is, however, a logical method of carrying off the discharges of a fistulous tract and has much to commend it.

Chemotherapy

Chemotherapy is justifiably credited with improving the results in gastrointestinal surgery. Anglem and Clute¹³ believe that it decreased the mortality rate in 75 consecutive cases of resections. They have reduced the amount of the drug used intraperitoneally from about 15 to about 5 gm. They dust the suture line with sulfanilamide powder and use some in the abdominal wall. The use of this method around the suture line has also been approved by Whipple.¹⁴

be withheld for fear of activation of the disease if indications for its use exist.

SUMMARY AND CONCLUSION

A case of pulmonary actinomycosis, in a patient with arrested pulmonary tuberculosis, is reported in which the sulfonamides apparently resulted in a cure.

The sulfonamides appear to be a valuable aid in the treatment of pulmonary actinomycosis, if not actually a specific cure. Iodides seem to be of less value than either sulfanilamide or sulfadiazine.

After this article had been submitted for publication, 2 cases of actinomycosis were reported in which sulfadiazine was the only medication employed.^{14, 15} In both, apparent cure of the disease was attributed to the sulfadiazine.

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MEDICAL PROGRESS

ABDOMINAL SURGERY

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BOSTON

RECENT advances in the field of abdominal surgery are numerous. They will be reviewed under a general heading and under others according to the involved viscus.

GENERAL CONSIDERATIONS

Anesthesia

The use of barbiturates in conjunction with other forms of anesthesia has been a popular development. Preliminary sedation has gradually changed from the morphine-and-scopolamine method toward more reliable and safer drugs. Avertin is being used much less extensively than heretofore, since other agents have proved to be more satisfactory.

In an attempt to determine the value of barbiturates in the reduction or delaying of shock under conditions of trauma similar to war wounds, Beecher, McCarrell and Evans¹ have reported the results of their experiments. In anesthetized animals, barbiturates delay shock from trauma producing dehydration or plasma loss, but not shock from hemorrhage. These authors further state that up to the time of the publication of their paper there were no data available to support the theory that barbiturates delay shock in the unanesthetized patient.

Anderson, Mousel and Mayo² have compared a group of patients operated on for lesions of the colon by two methods of supplementing spinal

anesthesia. When supplementary inhalation anesthesia was used, three times as many patients vomited and there was a 12 per cent mortality rate, whereas in a similar group of patients given a 2.5 per cent solution of Pentothal Sodium intravenously and 100 per cent oxygen by inhalation, only 5 per cent died. The average total amount of Pentothal Sodium given was slightly less than 1 gm. Quick recovery from anesthesia and absence of nausea were believed to play a distinct role in the better results.

This method has been used with and without oxygen at the Massachusetts General Hospital, and there seems to be little difference in the results unless the patient is nauseated early in the procedure. When this occurs, the addition of oxygen is of great benefit. It is probable that the total dose of Pentothal Sodium can be reduced by the use of oxygen, and also that there is a more rapid elimination of the drug. It is extremely desirable to prevent actual vomiting, since inspiration pneumonitis must be avoided. Oxygen inhalation appears to be harmless and probably should be used routinely in this combination.

Transverse Incisions

Transverse incisions are championed by Rees and Coller.³ They compare 225 patients operated on for abdominal lesions through transverse incisions with 346 in whom the vertical approach was used. Pulmonary complications occurred in 9.5 per cent of the transverse group, as compared with 26 per cent in the vertical. The incidence of dehiscence

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and hernia in scar was markedly less in the transverse group. These writers stress a great diminution in postoperative pain and discomfort. They state that Baudelocque¹ advocated the transverse approach nearly one hundred and twenty-five years ago, and used it in cesarean section.

Since Pfannenstiel,⁵ in 1900, advocated a transverse approach to pelvic surgery, there have been numerous advocates of some modification of the method to the abdominal cavity in general. Singleton and Blocker⁶ made an exhaustive study of the anatomical approaches to abdominal viscera in relation to wound disruption. Although their incisions were not quite what is interpreted as transverse, they were intended to accomplish much the same purpose. Gurd⁷ has strongly advocated the transverse approach to the exclusion of all others. Farr⁸ has also contributed much to the subject.

The use of transverse incisions has been adopted in some clinics with considerable regularity, whereas in others it has been used sporadically. At the Massachusetts General Hospital it is believed that many lesions are more easily handled through this approach. There are many patients whose wide-flaring costal angle make a transverse incision desirable for lesions of the upper abdomen. In the patient with a narrow, elongated costal angle, better exposure to the upper regions of the abdomen can be obtained through a long paramedian incision. With the use of nonabsorbable suture material, careful avoidance of nerve damage, absence of drainage through the wound, proper closure and the elimination of postoperative distention and vomiting, there will be less choice between the two methods.

Intestinal Trauma

Intestinal trauma during laparotomy has been properly condemned by Martland.⁹ He found the imprints of forceps, used by the surgeon in returning the small intestine to the abdominal cavity, at autopsy in 2 cases. In one case, 1500 cc. of blood that had come from such injuries was found in the lumen of the bowel. In another, he found more than forty of these imprints on the small bowel. In both cases, the surgeon had used a form of intestinal forceps devised for other purposes. They were of the kind that take a wide bite in the intestinal wall, producing a crushing defect that destroys the mucosa and submucosa. Such instruments are of little value for any purpose in intestinal surgery, and should never be used to grasp a segment of bowel that is not to be resected. Since instruments of this type are available, the only safe dictum seems to be to use no instrument in handling the intestine either during exploration or in returning the bowel to its natural position. Better anesthesia and the proper use of gloved hand and abdominal retractors will eliminate the need of a more traumatizing technic.

Drainage of Peritoneal Cavity

Drainage of the peritoneal cavity has been criticized by Cutler.¹⁰ It is amazing that there is still fixed in the minds of many surgeons the belief that the peritoneal cavity can be drained. When there is widespread abnormal fluid within the abdomen, it must be realized that adequate drainage to the outside is almost impossible to establish. The temptation is too great to resist, however, and is apt to lead to the establishment of some variety of foreign body from the depth of the cavity to the periphery. That a certain amount of the fluid contents surrounding the intestines can be led off for a short period of time is acknowledged. That these so-called "drains" not only fail to reduce the incidence of residual abscess but are an extra hazard, in that they form the basis of point obstruction to the bowel by adhesive bands, is obvious to all who have followed the course of these cases.

One does better to remove contaminated or irritating fluids, such as duodenal or gastric contents from acute perforation and bile, when such has escaped widely, by means of the suction tip. Closing the source of the leak is important if this has not already been spontaneously accomplished. In diffuse peritonitis of the inflammatory type seen in perforated appendicitis, one can seldom aid in the recovery by the establishment of drains to the gutters and the pelvis, as is so often practiced. Much can be accomplished by the drainage of a localized abscess or an area where leakage may take place. Care must be used to avoid contact with a suture line or it will leak in a disconcerting manner; also, material used for drainage must not come in contact with the small bowel.

Care should be used to place drains from the biliary system away from the main wound if possible. Needless wound infection, dehiscence and hernia in the scar can thus be avoided.¹¹ The suction method of Chaffin¹² has been used at the Massachusetts General Hospital to hasten the resolution of an abscess cavity. Our experience with this method in bile peritonitis has met with less success. It is, however, a logical method of carrying off the discharges of a fistulous tract and has much to commend it.

Chemotherapy

Chemotherapy is justifiably credited with improving the results in gastrointestinal surgery. Anglem and Clute¹³ believe that it decreased the mortality rate in 75 consecutive cases of resections. They have reduced the amount of the drug used intraperitoneally from about 15 to about 5 gm. They dust the suture line with sulfanilamide powder and use some in the abdominal wall. The use of this method around the suture line has also been approved by Whipple.¹⁴

Loria¹⁵ has compared the results in 100 consecutive cases of gunshot wound of the abdomen treated at the Charity Hospital in New Orleans. Forty-nine patients received chemotherapy, with a mortality rate of 18 per cent; 51 had no chemotherapy, and 51 per cent of them died.

All writers are in agreement that proper use of the sulfonamide drugs has been beneficial in dealing with surgical lesions prone to give rise to trouble from infection. The manner of use of these agents is changing as experience accumulates. In order to avoid some of the serious complications of the drug, it is well to weigh the evidence carefully. The relatively soluble sulfanilamide is absorbed from the peritoneal cavity with great rapidity. The transmission of large amounts of this drug through the portal system may account for the liver damage often noted. That many patients rapidly recover from jaundice that occurs is admitted, but if this concentration can be avoided it is obvious that the patient has less to combat in his fight for recovery. The less soluble drugs should probably not be used in the peritoneal cavity, since there must be some foreign-body reaction from them before absorption takes place.

The use of these chemical agents in abdominal wounds has met with less enthusiasm than formerly and probably will eventually be entirely abandoned. Although the bacteriostatic effect within the potentially contaminated wound may appear helpful in some cases, there has resulted delayed wound infection that is more troublesome than the earlier form noted before chemotherapy was known. It seems likely that delayed closure of the skin and fat layers, as emphasized by Collier and Valk,¹⁶ is a better method of meeting the situation.

Since it is known that a high concentration can be quickly obtained by the intravenous use of sulfadiazine and that tissue fluids carry essentially the same concentration as that of the blood stream,¹⁷ it seems likely that wide application of the principle is indicated. This method of chemotherapy in abdominal surgery, to the exclusion of all others, has been used at the Massachusetts General Hospital for over a year, and we are better satisfied with the results.

Femoral Hernia

Femoral hernia has been difficult to cure. The recurrence rate in most clinics is several times that for inguinal hernia. Moore¹⁸ reports on the results from the New York Hospital and recommends a new approach. An incision is made over the lower third of the inguinal canal, and dissection is carried deep and to the inferior border of Poupart's ligament. In this manner, the lower borders of the inguinal ligament and Cowper's ligament are adequately exposed. These structures can be approximated with three mattress sutures of silk in such a manner as effectively to close the femoral opening.

In 40 cases thus treated, there were no recurrences.

It is doubtful that the results by this method will prove to be any better than the commonly practiced procedure of closing the femoral opening by approximating the ligaments from the cephalward border of the inguinal ligament. That the new method requires less dissection is obvious, and it may be adopted to advantage by those who prefer to expose the femoral ring only from below.

STOMACH

Gastric Ulcer

Gastric ulcer has been analyzed by Judd and Priestley¹⁹ on the basis of treatment at the Mayo Clinic. They found that slightly less than half the patients treated medically had satisfactory results, whereas only 1 patient of 162 treated surgically was dissatisfied. None of the patients operated on developed anastomotic ulcer. The operative mortality was 2.5 per cent. Ten per cent of the cases diagnosed and treated as benign ulcer proved to be cancer.

This study is in accord with experience at the Massachusetts General Hospital.²⁰ We found our percentage of diagnostic errors to be 14 per cent. The mortality rate for gastrectomy for gastric ulcer is less than that for a similar procedure for duodenal ulcer because the duodenal stump creates no problem. We also found that cancer of the stomach, thought to be ulcer at the time of operation, gave a 40-per-cent chance of a five-year cure, as compared with a 21-per-cent chance in clinical cancer. It is our belief that gastric ulcer must be considered on a different basis than duodenal ulcer, and that the management of the two lesions is quite opposed. Duodenal ulcer is primarily a medical problem, whereas gastric ulcer is primarily a surgical one. If the term "peptic ulcer" could be abandoned, there would be less confusion. Too many cases of early cancer of the stomach are being treated as peptic ulcer, the true nature of the lesion being manifested only when cure is impossible.

Cancer

Cancer of the stomach continues to lead the list for deaths from cancer in this country. Greater attention must be given to the education of the public and of physicians concerning the early symptoms of this disease. So far, surgery offers the only method of cure. In spite of the increased scope of surgery, there still remain a large majority of these victims appearing too late for help.

De Amesti,²¹ of Santiago, analyzed 107 consecutive cases of cancer of the stomach personally treated. He was able to accomplish partial gastrectomy in 43 and total gastrectomy in 9. This is a higher resectability rate than can usually be carried out in such patients seen in the United States.

Pack and McNeer²² have collected 303 cases of total gastrectomy for cancer. The technic is now

well established, and there are undoubtedly hundreds of unreported cases. Members of the staff of the Massachusetts General Hospital alone have done more than 100 total gastrectomies. Eleven of these were high lesions involving the cardia and lower esophagus and were accomplished transthoracically. Many of these appeared unfavorable from the standpoint of nodal involvement and extension of the disease to neighboring structures. The mortality rate is lower than formerly, the extent of the procedure has increased, and the respites have well justified the effort.

Farris, Ransom and Collier²³ followed their patients surviving total gastrectomy from the standpoint of nutrition and hematopoiesis. Five of the 29 patients operated on since 1937 failed to survive the procedure, with only 2 deaths in the last 19. These writers state that there is no experimental evidence to support the clinical impression that pernicious anemia may follow total gastrectomy. They carefully checked the digestion in a woman of forty living for over four years after total gastrectomy. She did have a tendency to develop hypochromic microcytic anemia. The loss of the stomach, it is stated, interferes with the metabolism of iron, and anemia is easily controlled by the periodic administration of ferrous sulfate. The stomach does not play an essential role in the digestion of fat and protein. Glucose is absorbed more rapidly than normal in these patients. The mobility of the intestinal tract is finally decreased in spite of the fact that some of the patients have diarrhea immediately after operation. This is doubtless due to the tendency to feed carbohydrates in the early days. A high-protein and low-carbohydrate diet is recommended.

Balfour²⁴ found that gastrectomized rats did not gain weight on their usual diet. If, however, he fed them rat stomachs, their weight increased and their anemia improved.

Polypoid Lesions

Polypoid lesions of the stomach have been well analyzed by Spriggs and Marxer²⁵ in a complete issue of the British *Quarterly Journal of Medicine*. The differential diagnosis of true adenomatous polyps and polypoid gastritis is illustrated by case reports, drawings and roentgenograms. They include leiomyomatous lesions in their study. Attention is called to the neoplastic nature of true polypoid tumors as compared with the inflammatory origin of polyps found in gastritis. The ratio of malignant degeneration was lower than that found at the Massachusetts General Hospital²⁶ and by Pearl and Brunn.²⁷ The latter investigators, in a second analysis of the subject, have collected 84 cases of multiple gastric polyposis and added 3 cases of their own. In their group, as in ours, bleeding was the rule and achlorhydria was present in almost every case. In 19 of 37 cases with sufficient data, malignant

degeneration had occurred. This is higher than the 41 per cent of malignant degenerations found in our series. Although some of these cases, as well as those reported by Spriggs and Marxer, were followed for many years without evidence of cancer, it is agreed by all that resection of the involved segment is the rational treatment.

DUODENUM

Heuer and Holman²⁸ have challenged the usually accepted theory that the postoperative acid level in the stomach contents influences the result in patients subjected to surgery for duodenal ulcer. They have carefully followed a group of patients treated by gastroenterostomy and minimal, moderate and extensive resection. Many of the cases with a satisfactory result still had an acid level higher than normal. A greater proportion of satisfactory results were obtained by radical subtotal gastrectomy, but the series was small. Patients with anacidity or low acidity postoperatively had a 10 per cent greater chance of a satisfactory result than did those who continued to have a normal or higher than normal level. These writers justifiably question the rationale of the more radical procedures, and believe that there are other factors than the acid level that are responsible for the results.

Friedall, Shaar and Walters²⁹ found that 75 per cent of their patients subjected to partial gastrectomy for duodenal ulcer had a reduction in gastric acidity. Patients who had had previous perforation or had developed anastomotic ulcer following gastroenterostomy needed a more radical resection than did those without complications.

Church and Hinton³⁰ report the follow-up results on 104 cases of gastric resection for ulcer. The majority of these were for duodenal ulcer, although, unfortunately, some were for gastric and marginal ulcer, making deductions difficult. The cases were followed for an average of 2.9 years. The sex ratio was 9 males to 1 female. The ages varied from sixteen to sixty-nine. The average duration of pre-operative symptoms was eight years. Sixty-five per cent of the stomach was removed, including the duodenal ulcer. Sixty-six per cent of the patients were cured, 25 per cent were benefited, and 9 per cent were not relieved. Forty-six per cent had no free hydrochloric acid after operation, and some of these were in the unbenefited group.

Hinton³¹ believes that pain persisting in spite of adequate treatment and massive hemorrhage are the chief indications for surgery in duodenal ulcer. Intractability is, in fact, synonymous with unrelievable and persistent pain. He also believes that surgery is indicated in massive hemorrhage, regardless of the age of the patient, if continuous transfusion fails to improve the situation. He thinks that it is important to remove the segment of duodenum containing the ulcer, and has been able invariably

to include the ulcer site in the resection. This experience differs somewhat from that of others.

Lahey and Marshall³² have published an excellent article on the surgical management of duodenal ulcer. Their experience with ulcers in the second and third portions of the duodenum, as well as those with extensive inflammatory involvement, is in accord with that of most surgeons dealing with these lesions. One must be prepared to meet ulcerations of the duodenum that are not safely resectable.

Wangensteen³³ has used the idea proposed by Scrimger³⁴ and Estes³⁵ in closing the denuded antral segment. In 15 cases when he found the involved duodenum unresectable, he used the approved modification of the Finsterer exclusion procedure. After removing the mucosa from the antral segment, he approximated the remaining tissues face to face close to the pylorus by mattress sutures, instead of inverting them in the usual manner. This allowed him to trim away excess of the segment and to make a satisfactory leak-proof closure. He left room for an additional row of sutures along the cut edge, with no attempt at inversion. There were no complications in this series.

Andrus, Lord and Steffko³⁶ have reported their experimental and clinical experience with jejunal transplants to the stomach for the reduction of the hydrochloric acid level. In animals, this procedure was effective in every case. Five patients with duodenal ulcer were recently subjected to this operation, and the immediate results were satisfactory.

Colp and Druckerman³⁷ have used jejunostomy for feeding in 51 patients. These were preliminary in 6 cases and complementary in 38. There were no deaths from the jejunostomy, and these writers are enthusiastic over the benefits derived from it. They state that for this purpose, the pursestring type of jejunostomy is preferable to the Witzel type, which corroborates the opinion held at the Massachusetts General Hospital.

Lynn, Hay and Wangenstein³⁸ have had an unusually high percentage of difficulty from stasis in the duodenal loop following gastrectomy. One patient developed gangrene of the duodenum after resection of the stomach for carcinoma; 3 additional patients succumbed to the toxic effects of this loop, which failed to drain into the jejunum or remnant of the stomach. They devised a two-pronged nasal tube that was introduced into the stomach preoperatively. After the anastomosis is partially done, one prong of the tube is placed in the duodenal and the other in the distal jejunal segment.

Proximal jejunostomy for drainage of the stomach segment has been used at the Massachusetts General Hospital during the past year.³⁹ In 63 cases, this method obviated the need of the Levine tube in all but 3. In these failures, we are sure that the catheter left the stomach segment through the anastomosis and therefore failed to drain anything but duodenal contents. The patients like the method, and no

complications have arisen from its use. A No. 16 French double-eyed catheter is introduced through a pursestring opening in the distal jejunum approximately 15 cm. from the anastomosis. A lubricated stylet aids in its introduction 7 to 10 cm. within the stomach segment. The catheter is brought out through a tiny stab wound in the left side of the abdomen.

SMALL INTESTINE

Hinchey⁴⁰ reports 13 cases of gallstone ileus from the Salem Hospital. A seventy-nine-year-old woman survived two operations at intervals for this type of obstruction.

Wangensteen⁴¹ advises aseptic suction decompression enterostomy at the time of operation for gallstone ileus, and has applied this technic to emptying the small bowel in obstruction from other causes. The revival of the Monks's⁴² method was brought out by Cheever⁴³ several years ago. When the Miller-Abbott tube fails, the technic of Wangenstein has much to commend it. Many patients have been known to succumb to the toxins absorbed from unemptied, obstructed loops of small bowel after release of the obstructing focus.

A further report from the University of Minnesota Hospitals⁴⁴ on small-bowel obstruction emphasizes the importance of having this group of patients treated by special assignment. Their mortality rate has been reduced from nearly 20 to 7.4 per cent in the past year.

Smith and Van Beuren⁴⁵ report the results of treatment in 130 cases of acute ileus treated at the Presbyterian Hospital, New York City, from 1936 to 1939. This makes a consecutive report covering twenty-four years' experience in that clinic by the same authors. The mortality has decreased from 66.6 per cent in 1916-1919 to 23.8 per cent in the last series. Since the Miller-Abbott tube has been available, the mortality in 36 cases was 19 per cent; eliminating 4 deaths from paralytic ileus, there remained a 10 per cent mortality from mechanical obstruction.

Schottenfeld⁴⁶ has collected 275 cases of lipoma of the gastrointestinal tract, including 6 of his own; 56 per cent were in the small intestine, and 30 per cent in the ileum. Intussusception occurred in a large percentage of these. The mortality with intussusception from lipoma was 25 to 30 per cent. Three of his cases were found incidentally at autopsy, and 3 were operated on with recovery.

Gerwig and Stone⁴⁷ report a case of intussusception from a jejunal polyp and call attention to the rareness of polyps of the small bowel in comparison with those of the colon. They quote Lawrence,⁴⁸ who found 4 cases of polyp in both the small and large bowel in 232 cases of gastrointestinal polyposis that came to autopsy.

Keyes⁴⁹ again calls attention to the proper approach to fistulas of the small bowel. The operation

is done through a clean field, leaving a small segment of bowel containing the fistula to be removed later or left alone. This attack has much to commend it and can be made easier if a Miller-Abbott tube can be introduced to the point of the fistula. A second tube inserted in the distal limb is valuable if this can be done, since it makes the identification of the fistulous loop a simple matter.

Ginzburg and Garlock⁶⁰ review 77 cases of regional ileitis treated in their clinic. In 23 cases of ileocolic resection, there were 4 deaths. In 54 patients treated by ileocolostomy for exclusion of the diseased process, there were no postoperative deaths. Two patients in this group finally succumbed to sepsis; and 3 were subjected to late secondary resection of the diseased segment because of continued symptoms. In those having primary resection, 3 developed proximal involvement, whereas in the larger group only 2 acquired new areas of the disease. These writers conclude that exclusion by ileocolostomy is the procedure of choice and that the disease segment may be left alone unless it is a factor in continued disability.

Whipple⁶¹ reports 1 death in 23 ileocolic resections for regional ileitis with the preoperative and postoperative use of the Miller-Abbott tube.

Lahey and Sanderson⁶¹ in their recent article on right colectomy by the modified Mikulicz procedure report 1 fatality in 53 cases of regional ileitis treated by this method.

COLON

Singleton⁶² has written an illuminating article on the blood and lymphatic supply of the large bowel. The high incidence of abnormal blood supply, especially to the distal transverse and splenic colon, is of the utmost importance, particularly since the transverse colon beyond the midline may be devoid of anastomotic vessels from the left colic artery. Resection of this segment is likelier to result in gangrene of the remaining portion of bowel than is that of any other by the usual procedures. For this reason, one cannot depend on the types of operation that either fail to visualize the blood supply or limit the resection to the distal transverse segment.

Whipple⁶¹ believes that the preoperative and postoperative use of the Miller-Abbott tube has materially reduced his mortality in resections of the large bowel. Resections of the right colon for cancer in 16 cases in his clinic, without the aid of intubation, resulted in 3 fatalities, whereas in 41 cases in which the Miller-Abbott tube was used, there were only 4 deaths. From 1933 to 1937, resections in 38 cases resulted in 8 deaths, whereas from 1938 to 1942 there were only 7 deaths in 57 cases of resection. Experience and chemotherapy may have played some role, although most of the credit is given to decompression of the bowel by intubation.

Babcock⁶³ has devised new clamps for aseptic anastomosis in gastrointestinal surgery. This is the

so-called "one clamp" method and the instruments are a modification of the Rankin, Stone and Wangenstein varieties used for this purpose. Babcock reports resections in 65 serious and complicated cases — 35 of the stomach, with 4 deaths, and 30 of the intestine, with 4 deaths.

Fallis⁶⁴ reports the results in 31 cases of lesions in the lower sigmoid and upper rectum treated by anastomosis after the method described by Dixon.⁶⁵ The operation resulted in 2 deaths, and the complications were not extreme. Preliminary transverse colostomy is recommended. Stricture at the suture line was troublesome in some cases. Dilatation of the stricture was satisfactory in some, but permanent colostomy was finally resorted to in others. Drainage of the area is necessary because the suture line is below the peritoneal floor. Healing in this area is slower than it is in cases of peritonealized bowel.

Smithwick⁶⁶ states that 5 per cent of all people over forty years of age have diverticulosis of the colon. Of 333 patients hospitalized for diverticulitis, 64, or 19 per cent, were treated surgically. The best results were obtained by preliminary transverse colostomy. Resection and anastomosis of the diseased segment was best carried out from three to six months after the defunctioning colostomy.

Schnug⁶⁷ reports 6 cases of acute diverticulitis of the cecum, and collected 32 cases reported in the literature. All were diagnosed preoperatively as acute appendicitis, but in 1 resection was performed on the operator's diagnosis of cancer. Three lesions were removed locally, one was left alone, and one abscess was drained. Schnug believes that these lesions are best treated without surgical drainage or resection. The majority of the patients were under forty years of age. One third of them had had previous attacks. The lesions are usually solitary, and the mouth of the diverticulum can often be palpated through the cecal wall.

BILIARY SYSTEM

Gordon-Taylor⁶⁸ reports experimental data to refute the theory of the sphincter mechanism of the lower end of the bile duct. No circular muscular fibers can be found in this region. Only longitudinal and oblique fibers exist, and these are in the distal portion of the papilla of Vater. The action of these fibers, Gordon-Taylor believes, is partly to retract the papilla and partly to erect or aggregate the villous processes centripetally. By this action, duodenal reflux is prevented and the bile flow controlled. It is well to mention the value of the oblique direction of the duct through the duodenal wall, with overhang of mucosa often, if not always, present.

Gray and Sharpe⁶⁹ call attention to the probability that biliary dyskinesia is caused by remnants of the lower end of the gall bladder or cystic duct that are left during cholecystectomy. Of 44 cases studied, 26 had no residual stones; 7 of these were unrelieved

to include the ulcer site in the resection. This experience differs somewhat from that of others.

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of these patients have lived for twenty years post-operatively. Patients with chronic hemorrhagic purpura who do not respond to conservative therapy should be given the benefit of splenectomy. Also, in acute or fulminating hemorrhagic purpura that does not respond promptly to therapy, splenectomy should be performed before the patient's condition becomes critical. It is important to eliminate infection in the prevention of recurrent purpura. Splenectomy is the treatment of choice in hemolytic jaundice, particularly in children. It is preferable to perform the operation during a remission. In adults, splenectomy is not always necessary.

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after a second operation, and the authors question the original diagnosis of cholecystic disease. Complete relief was obtained in 11 of the 24 cases without stones that were followed. In 18 cases of residual stones, the stones were in the common duct in 11 cases, with complete relief in 6 and no relief in 4 of the 10 cases followed. In 7 cases with residual stone in the cystic duct, 6 were followed; 5 patients had complete relief, whereas 1 had none. The common duct was normally dilated in all cases with stones. Duodenal adhesions were frequent. Some patients had a degree of hepatitis and some had pancreatitis. Thirty-five patients had definite inflammation of the remnant of the cystic duct. No mention is made of instrumentation of the papilla of Vater in these cases. Two cases of residual stone in an inflamed cystic duct producing marked symptoms of biliary dyskinesia, which came on years after cholecystectomy, were recently seen at the Massachusetts General Hospital. In both cases, the common bile duct had not dilated normally, as it usually does after cholecystectomy. Both were relieved by the removal of the remnant of the cystic duct and a dilatation of the papilla to 6 mm. In both cases, the papilla was abnormally tight.

Dragstedt et al.⁶⁰ report a new technic for re-establishing continuity between the bile duct and the duodenum. A No. 18 French catheter is inserted in the hepatic duct a distance of 5 cm. This is implanted in the wall of the duodenum, after the method of Witzel, with silk technic. The catheter is then brought through the duodenal wall and led through its lumen and out again at some distance. In this manner, the bile is drained to the outside for ten days and the catheter is then removed. This resulted in a two-year cure in a thirty-five-year-old woman. These writers suggest that a similar procedure can be used in the pancreatic duct following resection of that region for carcinoma.

PANCREAS

The variability in behavior of the pancreatic remnant after experimental ligation of the duct is discussed by Dragstedt.⁶¹ In some animals the pancreas atrophied completely, whereas in others the structure was maintained. In those developing a complete fibrosis, the absence of lipocaic action on digestion was evidenced. Dragstedt proposed and carried out intubation of the duct with a ureteral catheter, which was led through the duodenal wall and out again, draining the pancreatic juice to the outside for a period of time. This he believes might improve the results in partial pancreatectomy for carcinoma.

Whipple⁶² discusses the subject and illustrates his present one-stage procedure for resection of the duodenum and pancreatic head for cancer. The end of the jejunum is anastomosed to the cut end of the bile duct. The cut end of the pancreas is implanted in the side of the jejunum, and the cut end of the

stomach is then anastomosed to the jejunum, end to side.

Phillips⁶³ reports a failure due to difficulty with the end of the pancreas and proposes a method similar to that suggested by Dragstedt and Whipple.

Rockey⁶⁴ cites a case of total pancreatectomy with death fifteen days later from bile peritonitis, owing to a leak from the cut end of the common bile duct. He believes that a patient may get on satisfactorily without any remaining pancreatic tissue, since the insulin needs are easily controlled. Lipocaic can be added to the diet.

SPLEEN

Sweet⁶⁵ adds 3 cases of true simple cyst of the spleen. He quotes Fowler,⁶⁶ who states that 21 per cent of 137 collected cases are of this variety. The differential diagnosis is discussed. All the patients are young and are conscious of a huge abdominal mass. The tumor feels cystic and is nontender. The roentgenograms give a characteristic picture.

Zabinski and Harkins⁶⁷ have collected 177 cases of delayed splenic rupture, including 4 cases of their own. This clinical syndrome, following trauma, is one that should always be considered in the differential diagnosis of the acute abdomen.

McLaughlin⁶⁸ encountered 30 cases of familial hemolytic jaundice during the last five years, and advised splenectomy in 16 because of clinical and laboratory evidence that the disease process was not latent. Thirteen patients who accepted this advice successfully underwent splenectomy. During operation and in the hour following there was a uniform rise in hemoglobin, which averaged 23 per cent. The red-cell counts correspondingly rose during this same period, with an average increase of 1,100,000 cells. Both the hemoglobin and cell readings fell gradually during the next two days and gradually increased to normal by the end of the first postoperative month. The leukocyte count also rose temporarily during splenectomy. There was no recurrence of the hemolytic factor in any of the 13 patients operated on. If hemolytic factors return after splenectomy, McLaughlin deducts that the original diagnosis was incorrect, that overlooked splenic tissue has become active or that hemolymph nodes have hypertrophied and have assumed a hemolytic character.

Eliason and Stevens⁶⁹ review the literature of the last ten years and give a statistical report showing the mortality and life expectancy following splenectomy in splenic anemia, thrombocytopenic purpura and icterioanemia. To this they add a report of 63 personal cases. Splenectomy gives the patient with splenic anemia the best chance for recovery, and the earlier in the disease it is performed, the lower is the surgical mortality and the greater the life expectancy. Eliason believes that splenectomy should be done even in the presence of cirrhosis. The operative mortality is approximately 10 per cent. Some

2 cc. of undiluted Type 18 rabbit serum, which was followed by a severe chill forty minutes later. Sulfadiazine was again administered. During the third week a loud harsh to-and-fro friction rub obliterating the normal heart sounds was heard in the third interspace just to the left of the sternum. The blood pressure was 90 systolic, 45 diastolic, and continued to be low, although the circulation in the extremities appeared to be satisfactory. He looked slightly cyanotic although he had not been given sulfadiazine for four days, during which period the temperature dropped to around 100°F. When the chemotherapy was resumed the temperature rose to 102°F. The pericardial friction rub cleared, although he continued to have chest signs suggestive of consolidation and pleural fluid. Three chest taps, however, were "dry."

During the fourth week, bronchoscopy revealed large amounts of thick sticky greenish-yellow secretion in the left bronchial tree. This was aspirated, leaving a slightly reddened but otherwise normal mucosa. The orifice of the left lower lobe appeared normal. The aeration of this lobe was much improved after aspiration, and it was planned to continue this procedure by means of an indwelling rubber catheter in the left main bronchus, which, however, the patient coughed up after fifteen minutes. His condition continued to be poor, and he raised large amounts of thick greenish-yellow material. A chest tap at the third interspace in the left midclavicular line yielded 100 cc. of sticky serosanguineous fluid from which a Type 18 pneumococcus was cultured. On the twenty-sixth day the pulse was paradoxical, with a rate of 140. The apex impulse was diffuse and tic-tac. A diagnosis of pericarditis with effusion was made, and a tap was attempted. No fluid was obtained, and it was thought that the pericardium was thickened. Three days later a roentgenogram of the chest showed practically no air in the left lung field. The right border of the heart was displaced farther to the right, and there were no visible pulsations along the right border with the patient in the horizontal position. A pericardiectomy was performed, with drainage of about 10 cc. of purulent material, which also yielded a Type 18 pneumococcus on culture. A biopsy of the pericardium showed acute and chronic inflammation.

The pericardial drainage continued to be copious, and it was believed that a large amount of chloride was being lost, the blood serum chloride being 86.8 milliequiv. per liter. The serum protein was 3.8 gm. per 100 cc. The patient was given a transfusion of 500 cc. of blood and 2 liters of saline, followed the next day by 500 cc. of plasma. Because of persistent fever, tachycardia and continued purulent pericardial drainage, the sulfadiazine was stopped and 15 cc. of penicillin (7500 units) was placed in the pericardial cavity.

On the thirty-seventh day a rib resection was performed, with drainage of 10 cc. of pus from an

empyema over the apex of the left lung. Because of the difficulty in maintaining adequate electrolyte balance, — the nonprotein nitrogen was 12 mg. per 100 cc., the chloride 98.2 milliequiv. per liter, and the protein 4.9 gm. per 100 cc., — he was given 10 cc. of adrenocortical substance. He was also given a total of 100,000 units of Type 18 anti-pneumococcus rabbit serum without any reaction. The next day he began to fail rapidly; in spite of being kept in an oxygen tent, he remained cyanotic and died the following day, forty days after admission.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES A. JANEWAY:* This case represents an unsolved bacteriologic problem. Here we have a man who from early life was unable to cope with infections that the majority of us could handle fairly readily.

An interesting point is that the patient went to an infirmary within a few hours after an attack of pneumonia began. He had density involving the whole left chest, and that is unusual for ordinary pneumonia in the first day. At such a time one may even have difficulty by x-ray in making out more than a small patch poking out from behind the heart. That to me is the first indication that something was wrong with this boy's lung other than what he came down with at the specific time.

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The past history is exceedingly interesting. He had had pneumonia five times within the preceding ten months, which is a most unusual story. I remember one patient, a boy with a nephrotic type of hemorrhagic nephritis, who in the course of two years had eight pneumococcal infections and four of these were due to Type 8. In the present case, the patient had a different lobe involved each time,

*Assistant professor of pediatrics, Harvard Medical School.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 30031

PRESENTATION OF CASE

A twenty-one-year-old college student who was spending a week end at the beach in midsummer awoke at five o'clock one morning, eight days before admission to this hospital, with severe knife-like pain in the left chest. He rapidly became feverish and within a few hours began to cough up rusty sputum. He took a taxi to the college infirmary, where x-ray examinations showed opacity of the entire left lung field. The sputum typing showed a Type 18 pneumococcus. With the administration of sulfadiazine, the pain, fever and discomfort gradually subsided during a period of seven days and then suddenly became worse, when he was transferred to this hospital.

The patient was reported to have had pneumonia five times within the preceding ten months. It was further alleged that a different lobe had been involved on each occasion and that a different type of pneumococcus had likewise been recovered in each of the various episodes.

The past history recorded the onset of mild diarrhea at the age of one and a half years, which persisted essentially without remission until the age of eighteen, when dilute hydrochloric acid was prescribed with complete and permanent relief. At the age of four and a half an adenoidectomy was performed. Two days later he developed a severe attack of pneumonia, and from that time on suffered one or two attacks of pneumonia every year. These were diagnosed sometimes as lobar and sometimes as lobular in type. At thirteen he had an attack of pansinusitis, when the gastric hypochlorhydria was discovered. At nineteen he had an attack of mild prostatitis that was persistent and failed to respond to sulfanilamide and massage.

The family history revealed that one grandmother was asthmatic.

Physical examination on entry was sketchy because of the patient's condition. The facies appeared anxious and drawn. He was in obvious distress, with labored grunting respirations and com-

plete splinting of the left side of the chest. There were patchy dullness and bronchial breathing in the upper portions of the left chest; over the area of the left lower lobe there were dullness and absent breath sounds. The heart was not enlarged, and there were no murmurs; the pulmonary second sound was greater than the aortic. The abdomen was flat and soft, and no masses or tenderness were made out. The mucous membranes and nailbeds did not appear cyanotic.

The rectal temperature was 103°F., the pulse 120, and the respirations 30.

An x-ray film of the chest taken with a portable machine the day after entry showed the following: "There is hazy density occupying the lower half of the left lung field. The left diaphragm is elevated, and the heart and mediastinum are not displaced. The right lung field is clear. Comparison with a film taken several days before at the college infirmary shows considerable clearing." The following day fluoroscopy showed a triangular area of density involving the midportion of the left lower lobe, which was interpreted as either atelectasis or fluid. Another film from the infirmary, taken four months before entry, after clinical recovery from his last attack of pneumonia, showed incomplete expansion of the left lower lobe.

Laboratory studies at the time of entry showed a hemoglobin of 13.0 gm. and a white-cell count of 14,800, with 75 per cent neutrophils. The urine had a specific gravity of 1.010 and contained no albumin or sugar; the sediment was free from red cells, crystals and casts. A blood Hinton test was negative. The blood sulfadiazine level was 3.5 mg. per 100 cc. Three sputum examinations showed alpha-hemolytic streptococci but no pneumococci. Two blood cultures were negative. The sulfadiazine dosage was increased to 6 gm. per day, and a blood level of 6.2 mg. per 100 cc. was obtained. On this regime the temperature fell to normal on the fourth day and, with one exception, remained normal for six days, the sulfadiazine having been stopped on the fourth day of normal temperature. Physical examination showed complete clearing of the upper lobe and improved aeration of the lower lobe.

On the eleventh hospital day the patient complained of sharp inspiratory pain over the anterior left rib margin and a sensation of chilliness. The temperature rose to 101°F, the pulse from 80 to 110, and the respirations from 20 to 30. There was no change in physical signs, however, and an x-ray film taken with a portable machine was interpreted as showing improvement since the last examination. A sputum examination showed mucopurulent material without blood staining, and from it a Type 18 pneumococcus was grown in pure culture. A few days later, however, a roentgenogram showed a marked change — the development of hazy density obscuring the entire left lung field. After a negative conjunctival serum test, the patient was given

*On leave of absence

1 cc. of undiluted Type 18 rabbit serum, which was followed by a severe chill forty minutes later. Sulfadiazine was again administered. During the third week a loud harsh to-and-fro friction rub obliterating the normal heart sounds was heard in the third interspace just to the left of the sternum. The blood pressure was 90 systolic, 45 diastolic, and continued to be low, although the circulation in the extremities appeared to be satisfactory. He looked slightly cyanotic although he had not been given sulfadiazine for four days, during which period the temperature dropped to around 100°F. When the chemotherapy was resumed the temperature rose to 102°F. The pericardial friction rub cleared, although he continued to have chest signs suggestive of consolidation and pleural fluid. Three chest taps, however, were "dry."

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and with a different type of pneumococcus. One must assume that there was something obviously wrong in that he was unable to resist infection with the pneumococcus. That is an unexplainable situation, so far as I know, in terms of present bacteriologic knowledge, but it is not too uncommon a story. Some persons have furuncles and develop a generalized staphylococcal infection with osteomyelitis. Others are prone to repeated occurrences of lobar pneumonia, and then there is the group best exemplified by children with rheumatic infection, who are constitutionally unable to handle infection with the hemolytic streptococcus. When we go into the past history of this boy we know that he had an attack of mild diarrhea at one and a half years and that this continued until the age of eighteen, when he was given hydrochloric acid. That again suggests some sort of constitutional defect, because hypochlorhydria or achlorhydria is not common at that time of life and perhaps represents a true functional deficiency of the stomach.

This patient's troubles began at four and a half years, when his adenoids were removed. Two days later he developed pneumonia, and from then on had one or two attacks a year. These were diagnosed sometimes as lobar and sometimes as lobular in type, which does not matter; presumably they were pneumococcal infections, although we do not know. At thirteen he had an attack of pansinusitis, another common form of pneumococcal infection, although it might have been streptococcal. At nineteen he had prostatitis, which was persistent and failed to respond to sulfonamides and massage. This is not at all unusual in patients prone to repeated attacks of upper respiratory infection, and no one can say to what it is due. But all these things point to a person who has a low resistance to infection in general, and particularly to infection in the respiratory tract caused by the pneumococcus.

On entry there were dullness and absent breath sounds in the left lower lobe, and x-ray examination showed hazy density of the lower half of the left lung field, with elevation of the diaphragm on the left. This is in contrast to the picture taken on entry to the infirmary, when he had density involving the whole chest. One is forced to the conclusion that something was wrong with the left lower lobe. Perhaps the process in the upper part of the chest had cleared on sulfadiazine therapy.

May we see the x-ray films?

DR. GEORGE W. HOLMES: To discuss these films completely would take the whole hour. The patient had repeated attacks of pneumonia, and one wonders whether or not there was some trouble in one of the bronchi. Apparently someone else thought of that, since lipiodol was injected into the bronchi. From this film I cannot say definitely that he had or had not any trouble with the bronchi. It is not the usual picture of bronchiectasis; yet it is not quite normal.

Another thing that is fairly striking about the case is that the heart shadow became progressively larger. Whether he developed fluid in the pericardium or whether the change was due to longstanding intrapulmonary pressure, I cannot tell. Another unusual thing is the development of this density, which includes the entire lung. There is no evidence that the mediastinum was displaced or that the heart was pushed to the right.

DR. JANEWAY: Do you not believe that the heart was being pushed to the left?

DR. HOLMES: I cannot answer that definitely, but my feeling is that there was no change in the position of the heart and mediastinum.

Another point is that the process extends to the extreme apex, which is unusual in the presence of fluid. It is seen, however, with complete consolidation of the lung or with tumor. This process comes and goes, and that is hard to explain. Fluid to that extent should displace the heart in the opposite direction. I should think that this was consolidation.

DR. JANEWAY: I think that one can skip through the remainder of this patient's course fairly rapidly. He entered the hospital, as I have said, apparently with considerable change from the first film to the second. Probably the most satisfactory explanation is that he had pneumonia involving the upper portion of the lung. He was treated with sulfadiazine, and most of the process cleared; but a residual was present in the lower lobe, where there were dullness and diminution of the breath sounds. Another thing that strikes me on looking at these films is the contrast between the rib shadows on the two sides; they are drawn closer together on the left than they are on the right. One does not see that in this film, which suggests that later on there was some collapse of the left lower lobe. By increasing the dose of sulfadiazine in a fairly short time the temperature was again brought down and there was clearing of the picture. Therefore, one must assume that because of insufficient therapy he had a relapse of pneumonia, which brought him to the hospital. Although more intensive chemotherapy aborted the infection, it obviously did not cure the patient.

From then on the story is that of someone with complications of pneumococcal pneumonia. After several days of normal temperature he had a second return of symptoms. There were inspiratory pain, pleural pain over the left rib, chills and a rise in temperature, with no change in physical signs. As one watches the course, it seems likely that this was a different sort of relapse from the first one, which was perfectly compatible with a relapse of the pneumonia. This time, I believe, purulent complications were beginning to develop in the left chest, because, from then on, sulfadiazine therapy was relatively ineffectual.

During the third week the patient had a to-and-fro friction rub, with a fall in blood pressure and slight cyanosis. This was accompanied by en-

argement of the heart, as Dr. Holmes has pointed out. There was not the slightest doubt that this boy had pericarditis, which, as you all know, is one of the most serious complications of lobar pneumonia, and formerly occurred in a fair percentage of cases. Here is a boy with almost no resistance to organisms who, in the presence of not too effective chemotherapy, went on to develop some type of purulent complication. An attempt was made to give serum therapy; possibly that should have been done earlier because obviously the boy did not handle pneumococcal infection too well. We do not know whether he had antibodies at the time the serum was given. Presumably he did or he would not have shown much in the way of focal complications. Another factor is that at that time the temperature went up when he was given sulfadiazine and stayed up when it was taken away. As a result of chemotherapy this boy had become sensitive to sulfadiazine, which further complicates the picture.

Another complication was present; this patient eventually had a rib resection because of an empyema, which was evidenced by the aspiration of a sticky purulent secretion, containing a Type 18 pneumococcus, from the region of the left lower lobe.

Perhaps the only intelligent way to put this all together is to say that there was some abnormality that rendered the left lower lobe peculiarly vulnerable, but this vulnerability to pneumococcal infection was probably on the basis of something constitutional, because the patient had had infections everywhere. Another point is that for some reason, possibly because of the development of a small abscess or because he developed a real bronchial occlusion as suggested by the pulling together of the ribs on the left side, chemotherapy, when given to him the first time, perhaps inadequately, failed to cure the infection. There is little question that there was some occlusion on the left because the bronchus contained sticky secretion, and because the infection in the left lower lobe never cleared up. Whether he had bronchiectasis, abscess or an unresolved pneumonia that flared up when the sulfadiazine level fell, I cannot tell.

I should say that at autopsy they found not only empyema and pericarditis but also pneumococcal infection in the left lower lobe, probably some bronchial constriction and therefore abscesses or some fibrosis and collapse. Why the boy died when he did I do not know, but I suspect that it was due either to the pericarditis or to the empyema, which did not respond to drainage. Possibly the infection broke into the peritoneum and produced peritonitis, but I doubt that.

Dr. JOHN CASS: I attended this boy during the week before he came in here and there was no doubt in my mind that he was having another one of his series of acute pulmonary infections, with an underlying disease of a chronic nature. He did quite well for a few days, and then his lungs filled up again and

he was admitted to this hospital. The day before he had had a blood sulfadiazine level of 8 mg. per 100 cc. The next morning the level was 3.6 mg., and we pushed the dose up until it reached a peak of 13 mg. He had an essentially normal temperature for three days except for one time when the sulfadiazine was stopped. At a level of 5 or 6 mg., he flared up again, and we immediately gave more sulfadiazine and kept him at a level of around 8 mg. for the next week. Then, the chest signs changed definitely overnight, an area of complete consolidation appearing. This same thing had happened in one of his previous attacks, when he had flared up overnight with consolidation of the left upper lobe.

The important thing was to get this boy over the acute disease. We all recognized that he had underlying chronic pulmonary disease, presumably bronchiectasis. We did everything that we could. We gave serum when he flared up again under sulfadiazine. He had a severe chill and was pulseless for a few minutes. With the first chill the temperature went up to 106°F., but the next day it fell down and stayed down for two days; then it started to go up again. Dr. Maxwell Finland saw him, and the question was raised whether to give serum again and stop the sulfadiazine. He had seen the boy several times during the previous year. He was not impressed with the Type 18 pneumococcus as the etiologic agent. We again tried sulfadiazine, bringing up the level as high as before, over 10 mg., without any effect. We pushed the sulfadiazine level higher by giving the drug intravenously, gave more serum and drained the empyema and the pericarditis. The chest signs did not change materially, and we believed that one lung was free of infection.

The patient died in a state of anoxemia. He was blue and that was the thing that made us realize that we were not dealing with a unilateral disease. He was cyanotic at all times except for three or four hours after the bronchoscopy, when air got into the lower left lobe for a few hours. We did not have the courage to subject him to bronchoscopy again. He was given oxygen and a mixture of helium and oxygen both by mask and by tent. Our diagnoses were the same as those of Dr. Janeway; we believed that the boy died of lobar pneumonia, with empyema, pericarditis and an underlying chronic diffuse pulmonary disease, probably bronchiectasis.

Dr. JANEWAY: Did he have a reaction the second time serum was used?

Dr. CASS: No.

CLINICAL DIAGNOSES

Lobar pneumonia (Type 18 pneumococcus).
Pericarditis.
Empyema, left.
Bronchiectasis: left lower lobe?

DR. JANEWAY'S DIAGNOSES

Lobar pneumonia (Type 18 pneumococcus): left upper lobe.
 Pericarditis (Type 18 pneumococcus).
 Empyema, left (Type 18 pneumococcus).
 Bronchial constriction and atelectasis, with infection (Type 18 pneumococcus): left lower lobe.

ANATOMICAL DIAGNOSES

Bronchiolitis fibrosa obliterans.
 Bronchopneumonia.
 Bronchiectasis, left lower lobe.
 Pericarditis, acute, fibrinopurulent.
 Empyema, left.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: At autopsy this man still had 10 to 15 cc. of pus in the pericardial cavity and some empyema. At the base of the drainage tube, over the visceral pleura, was a huge pocket of

ference, so that there was definite bronchiectasis in the left lower lobe. The right lung, although not collapsed, was also encased in a thick fibrous pleura and on section showed a similar sprinkling of tubercle-like lesions throughout all lobes.

On microscopical examination of the left lung we found that the bronchioles were filled with exudate and that the walls were destroyed in places. There was also a great deal of organization of the exudate within the bronchi and bronchioles, especially in the smaller air sacs or alveolar ducts (Fig. 1). Immediately surrounding the bronchi there was evidence of recent infection. This reminded us of a condition called "bronchiolitis fibrosa obliterans," which was described by Lange¹ in 1901 and again fifteen years ago here in Boston by Blumgart and MacMahon.² The latter described 5 cases which simulated miliary tuberculosis but in which, of course, there was no evidence of tuberculosis. We were able to find similar bronchiolitis with fibrous-tissue plugs in the right lung, with a more acute pneumonic process around

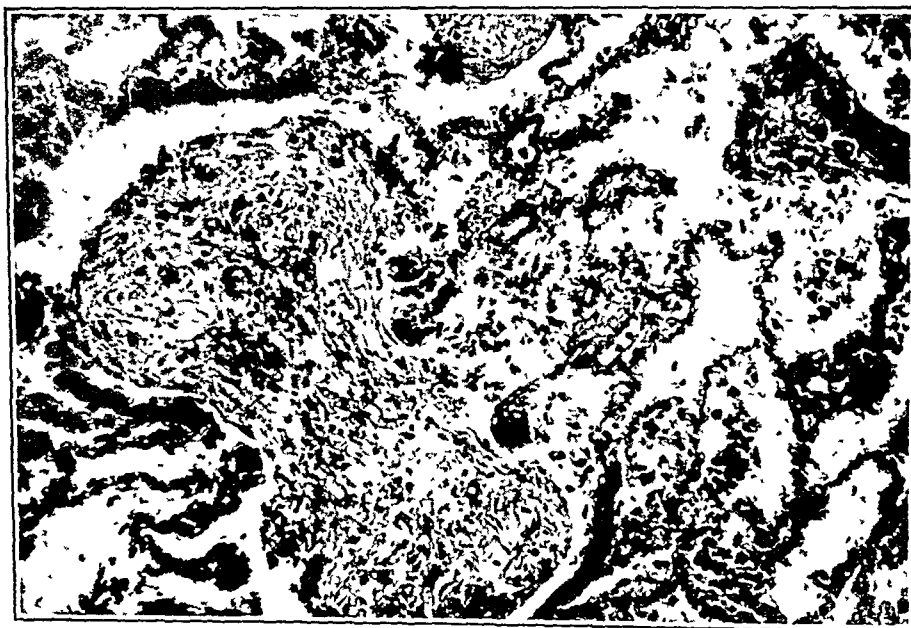


FIGURE 1. Photomicrograph Showing Bronchiolitis Fibrosa Obliterans of an Alveolar Duct.

pus. The left lung was encased in a fibrous pleural capsule 1 to 2 mm. in thickness, and the whole lung itself was shrunken to about two thirds its normal size. On sectioning the lung there were numerous grayish granular foci 1 to 2 mm. in diameter that looked like miliary tuberculosis, and at the time of autopsy the diagnosis lay between tuberculosis and lobar pneumonia with small abscesses. In the left lower lobe the larger bronchi were filled with thick, tenacious material so that it would have been quite impossible for air to get through. The smaller bronchioles were also filled with this material and were distended to perhaps 0.5 cm. in circum-

ference. The disease on the right seemed to be definitely more recent than that on the left, but the fundamental chronic process was the same.

The question arises whether this was the result of an organizing pneumonia and something that he had had for a long time or whether it was the disease entity that had precipitated the attacks of pneumonia. We have seen the same condition a number of times. This morning I looked through our files and found that we have made the diagnosis of bronchiolitis fibrosa obliterans seventeen times. It is interesting that in 5 of the 17 cases the patients had heart disease. Two of these were rheumatic in

origin, which is interesting in view of the fact that an organizing bronchiolitis has been described as a form of rheumatic pneumonia by Masson et al.³ The other 12 cases were associated with pneumonia, organizing pleuritis, empyema or pericarditis, 2 of them occurring in patients with nephritis. Perhaps this is not a disease entity in itself but a nonspecific finding that develops with a diffuse organizing pulmonary infection caused by a variety of etiologic agents. For example, the pulmonary complications of the victims of the Cocoanut Grove fire who died after admission into the hospital showed an acute necrotizing bronchiolitis.⁴ Those who had severe pulmonary damage and survived may well have developed varying degrees of bronchiolitis fibrosa and perhaps will be relatively nonresistant to future pulmonary infections.

In the later stages of the disease, failure of the right side of the heart may occur. This was true in the present case, the right ventricular wall being twice its normal size. There was no evidence of disease in any other organ.

DR. JANEWAY: If you assume this was a chronic process and not one that began with this particular infection, how can you reconcile that with so little change in the earlier x-ray films?

DR. HOLMES: I do not know exactly how much these cases of the type described show on x-ray, but I should certainly say that these films showed nothing abnormal except for the character of the lipiodol shadow in the left descending bronchus. That is abnormal, but it is not characteristic of bronchiectasis.

DR. CASTLEMAN: The right lung was encased in a thickened pleura that certainly antedated the recent disease.

DR. ALLAN BUTLER: If the patient had had bronchiolitis fibrosa obliterans previous to the last attack, then I should think that decreased aeration of the lung would have been noticed clinically and that he would have complained between times of dyspnea.

DR. CASS: He had not been well since he was four years old. The only exception to that was the three years spent in Arizona, and he was not active out there. He never completed a full year of school and really never did anything, just lived the life of an invalid. The first time I saw him he was cyanotic.

DR. JANEWAY: How about the kidneys?

DR. CASTLEMAN: They were normal.

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CASE 30032

PRESENTATION OF CASE

A fifty-four-year-old clerical worker entered the hospital because of "asthma" of three weeks' duration.

The patient was in good health until five months before admission, when she developed a severe steady pain in the lower sternum associated with and aggravated by an "awful" nonproductive cough. These continued for two to three weeks. About two months before admission she coughed up frothy white material flecked with blood for three days. She developed a "severe strain" between the scapulas. An x-ray film of the chest was said to have shown "adhesions between the lung and the diaphragm, clearing pneumonia and thickening of the pleura." She remained at home for six weeks without any relief. In the meantime her appetite declined and she developed abdominal and lower costal pain which she attributed to continuous coughing. Three weeks before entry she developed wheezing respirations and a filled-up feeling, in addition to the cough and pain. The cough was productive of a slightly odorous white froth with no thick exudate. The "asthma" improved slightly and the chest pain subsided. There was no fever, chills or night sweats, sinus pain, toothache, sore throat, hay fever or hives. She had had no upper respiratory operations, and there was no history of aspiration of a foreign body. The weight had remained constant until the three weeks before entry, when she had lost about 7 pounds. There was no history of a tuberculous contact.

Physical examination showed a well-developed, well-nourished, slightly dyspneic woman in no distress. There was no nasal obstruction. The "tonsillar nodes" were slightly enlarged and nontender. The diaphragm was in normal position and showed slight mobility. In the lungs there were scattered coarse, sticky rales, a few moist rales and rare sibilant rhonchi. The heart was normal. Examination was otherwise not remarkable.

The blood pressure was 120 systolic, 90 diastolic. The temperature was 98.6°F., the pulse 120, and the respirations 26.

Examination of the blood showed a red-cell count of 4,860,000. The white-cell count was 11,600, with 86 per cent neutrophils. The urine was negative. The blood sedimentation rate was 2 mm. in fifteen minutes and 22 mm. in sixty minutes. A blood Hinton test was negative.

X-ray examination of the chest showed a generalized increase in the lung markings, with diffuse haziness over the lower two thirds of the right chest and to a lesser degree of the left chest. A grid film revealed numerous small areas of diminished density having the appearance of bronchiectatic changes. The right diaphragm was adherent anteriorly. The

heart was not grossly enlarged. The aorta was tortuous and displayed calcification of the arch.

For the first few days she experienced considerable respiratory distress. She was orthopneic and wheezed heavily. There was no relief from adrenalin, but a certain amount of temporary relief from aminophyllin. She was given 1 gm. of sulfadiazine on the third day, followed by 2 gm. daily for the next six days. On the fifth day the blood sulfadiazine level was 3.8 mg. per 100 cc.

Bronchoscopy on the eighth day showed marked spasm of the vocal cords. The trachea was narrowed in the anteroposterior direction. The carina was thickened and shortened in the anteroposterior diameter, giving it a twisted rope-like appearance. The right bronchus was also narrowed in the anteroposterior diameter and had a similar appearance, which was thought to be due to spasm. On the medial wall of the right main bronchus close to the carina there was a thickening of the bronchial wall that bled easily. A biopsy was attempted but no tissue could be obtained. The left main bronchus had much the same narrowed spastic appearance as the right.

Following bronchoscopy the patient became slightly more dyspneic and cyanotic. Bronchography had to be omitted. She was given 10 cc. of aminophyllin with temporary relief. In the next twenty-four hours she experienced considerable respiratory distress and raised large amounts of blood-tinged, frothy sputum. The respirations were 36, the pulse 140, and the blood pressure 140 systolic, 90 diastolic. On the ninth day coarse rattles were heard over the left chest and the patient was pale, sweaty and cold. The administration of aminophyllin was ineffective, and oxygen gave only temporary relief. She became progressively more dyspneic and died suddenly on the tenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. PAUL C. ZAMECNIK: The first problem to decide in reaching a diagnosis in this case is whether the disease involving the bronchial tree was intrinsic or extrinsic in origin. Since both the right and left main stem bronchi presented the same narrowed, spastic appearance, and inasmuch as both sides of the chest showed diffuse haziness by x-ray, even though it was more marked in the right chest, the evidence points toward intrinsic disease of the bronchi and bronchioles.

An extrinsic mediastinal mass would, in general, be more likely to produce bronchial stenosis unilaterally rather than bilaterally. It is true that lymphomatous mediastinal nodes can produce bronchial obstruction of both sides of the chest, but lymphomatous masses of this magnitude are usually visible by x-ray, and in this case no mediastinal enlargement is reported. Such additional possibilities as a dermoid cyst, a neurofibroma, a substernal

thyroid gland, and an enlarged thymus fall into the category and therefore have no positive evidence to support them. In connection with the possibility of aortic aneurysm, the x-ray definition of the aorta with its tortuosity and calcification seems sufficiently clear to make this diagnosis unlikely. Furthermore, the aortic second sound was presumably intact, and the Hinton reaction negative.

A discussion of intrinsic diseases involving the bronchial tree may properly be introduced by a consideration of bronchial asthma and bronchiogenic carcinoma. Against the diagnosis of bronchial asthma are the age of the patient at the onset of the disease, the lack of a previous history of asthmatic attacks, the failure of response to epinephrin, and the rapid, downhill progress of the disease. The spasm of the bronchi and the bronchiectasis, however, fit in well with this diagnosis. It is impossible to rule out bronchiogenic carcinoma, but the bilateral character of the disease and the absence of visible neoplasm by bronchoscopy rob this diagnosis of its chief support.

If this line of reasoning is correct, one is left with certain rarer diseases involving the trachea, bronchi and bronchioles. Scleroma is usually a more chronic type of disease than the one here presented, starting with a falling in and a fibrous-tissue replacement of the cartilaginous framework of the nose and throat; then the glottis and trachea are involved and the process extends downward in the respiratory tract. There is no such antecedent history in this case, and indeed the history suggests that the difficulty progressed upward from the lower part of the respiratory tract.

Most of the data are consistent with a disease in which connective tissue grows in from the walls of the terminal and even the larger bronchi, with a resultant partial or complete occlusion of their lumens. Such a condition occasionally follows pneumonia or acute bronchitis, and is characterized by a progressively downhill course, with dyspnea, orthopnea, cough and fatal termination. In most cases of bronchiolitis fibrosa obliterans, miliary nodules resembling those of tuberculosis are seen in the lung fields by x-ray, but in the present case no mention of such findings is made. In spite of the absence of this valuable sign, I find myself forced to make this diagnosis. The initial chest pain may be attributed to pleural adhesions accompanying the pneumonia, and the remainder of the picture appears to have been due to obliterative bronchiolitis and bronchitis, with bronchiectasis.

CLINICAL DIAGNOSIS

Bronchial asthma.

DR. ZAMECNIK'S DIAGNOSIS

Bronchiolitis fibrosa obliterans.

ANATOMICAL DIAGNOSIS

Carcinoma of pancreas, with metastases to lungs, pleura and bronchial, mediastinal and retroperitoneal lymph nodes.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: This case is another example of Dr. Rackemann's frequent statement "All is not allergy that wheezes," and Dr. Amechnik wisely discarded the diagnosis of bronchial asthma, although that was the ante-mortem diagnosis. There was disease of the bronchial tree, but it

was primarily extrinsic. The autopsy showed diffuse carcinomatosis of both lungs, and microscopically the tumor cells involved the lymphatics, especially in the peribronchial and peribronchiolar lymphatics. In some places tumor cells had extended through the bronchiolar walls and had invaded the mucosa. We were unable, however, to find any gross evidence of a tumor that involved the lumen of a bronchus, and we did not believe that the primary tumor was in the lung. We found metastases in the bronchial and retroperitoneal lymph nodes and finally discovered the primary tumor in the body of the pancreas.

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MUTATIS MUTANDIS

CHANGE begets change. Not so long ago it was generally accepted that unconsciousness following a blow on the head — concussion — and the more serious pathologic changes often associated with it were the direct result of the local application of force. This did not explain, however, the damage to the brain opposite the point struck. Because this damage was usually severer than that occurring immediately beneath the point of contact it could not be ignored, and the theory of contracoup was evolved to explain its presence. It was conceded that acceleration or deceleration of the head was necessary to produce the contracoup effect but did not necessarily cause unconsciousness. More recent work done with greater exactness under experi-

mental conditions has also included acceleration or deceleration of the head as a prerequisite of unconsciousness. As a corollary to this point of view the failure to lose consciousness following perforating wounds of the skull, wounds made by multiple small missiles with low velocity or a crush of the head was alleged to be traceable to an absence of acceleration or deceleration of the skull and its contents. These conclusions have been rather widely accepted and they have been regarded as a satisfactory and probably a final explanation of the mechanism of concussion and its associated brain pathology.

Now comes a physicist, a Doctor of Philosophy from Oxford and the holder of an M.A. degree from Edinburgh, who, working as a research physicist in the Laboratory of Physiology and the Department of Surgery at Oxford, propounds a new explanation for the development of unconsciousness and the causation of all degrees of brain injury.* In the course of his paper he claims that neither the contracoup nor the acceleration-deceleration effect is adequate as explanation for such results. He states that the most important physical properties of the brain are its comparatively uniform density, its extreme incompressibility, the small resistance it offers to change in shape as compared with the skull which it offers to change in size (the effect of pressure by a retractor as compared with that of an estimate pressure of 10,000 tons), and the lesser rigidity of the brain as compared with that of the skull — 1 ton being required to reduce the diameter of the skull by 1 cm. Furthermore, he asserts that the shapes of the skull and brain determine the location of the injuries. He also points out that if one grants that the brain behaves like similar substances whose physical properties have been studied to date, its constituent particles are pulled so far apart as the result of a blow that they do not join up again properly when the immediate effect of the blow is over. The amount of this pulling apart is proportional to shear strain or rotational effect, and not to the amount of compression that occurs.

In conformity with this conception and working with a model constructed of materials that are claimed to react to blows in the same way that the skull and brain do, the author claims to have demonstrated that the localized damage in cranial cerebral injuries is traceable to skull distortion

*Holbourn, A. H. S. Mechanics of head injuries. *Lancet* 2:438-441 1943.

Distant damage, on the other hand, occurs in regions where the brain is locally fixed in relation to the skull. Adjacent cerebral tissue is thus permitted to rotate around such fixed points and to set up shear strains, which eventuate in the pathologic changes recognized as concussion, contusion and laceration. Extradural hemorrhages are said to be caused by skull distortion, whereas subdural and subarachnoid hemorrhages result either from this same cause or from shearing damage to appropriate blood vessels.

To produce shear strains, therefore, the skull and its contents must not only be struck but must also be rotated. Because of its shape the liability of compression without rotation of the skull and its contents following a blow is extremely small. On the theoretical concept that concussion with its unconsciousness is caused by separation of constituent particles to a minimal degree, in contradistinction to a laceration, when such separation is maximal, the author predicts, "The theory of head injury can be developed on the assumption that during and immediately after the blow, all factors other than the purely physical can be neglected." This includes so-called "contracoup damage." If further investigations support his demonstration, then, as he says, "One can be reasonably confident that only minor modification to the theory will be necessary to explain quantitatively the usual type of accident" — at least until another worker presents a new concept and a different explanation.

A NEW TEST FOR ACUTE BACTERIAL INFECTION

THREE chemical constituents of pneumococci are well known: the type-specific polysaccharides, the species-specific protein and a nonspecific carbohydrate. The last is apparently common to many bacteria, and recent work has shown that a protein substance reacting with this nonspecific carbohydrate is present in human serum during the acute phase of many bacterial infections but is not found after recovery, nor is it present in the serum of normal individuals. Skin tests with the type-specific polysaccharide have had a limited use, especially before the introduction of chemotherapy, both as an aid in prognosis and as a guide to therapy with antipneumococcus serum. Satisfactory preparations of both the specific and nonspecific carbohydrates

are difficult to make, and skin reactions with these substances, as with other materials, have many drawbacks.

Löfström* in a monograph just published in Sweden describes in detail a nonspecific reaction that involves the capsular swelling of pneumococci of certain types in human serum. The Type 27 pneumococcus has proved to be most satisfactory for this purpose. The reaction is carried out in exactly the same manner as the Neufeld test for the typing of pneumococci. In the latter test the pneumococcus in question shows swelling of the capsule when it is mixed with antipneumococcus rabbit serum of the homologous type. Löfström's reaction takes place with the Type 27 pneumococcus (and to only slightly less extent with Types 16 and 28) and human serums from a large variety of conditions. The author has worked out many of the physical and chemical characteristics of the serum responsible for this reaction and has applied it to the study of serums from a variety of conditions.

A number of important practical applications of this nonspecific reaction are claimed by the author. It does not occur in the serum of normal individuals but is present only during the febrile stage of bacterial infections and in some other febrile conditions associated with tissue breakdown. It cannot be demonstrated in the virus diseases that he has studied. Thus the reaction is negative with serums from patients with common colds or influenza, but becomes positive if bacterial complications intervene. The reaction occurs during acute bacterial infections of the respiratory tract, such as tonsillitis, sinusitis and pneumonia, but promptly disappears from the serum after the acute infection subsides. It is therefore offered as an aid in prognosticating the occurrence of bacterial complications of virus infections or other conditions. In cases of meningitis in which cultures are negative the test may be used to differentiate bacterial from virus infections — it is positive in all the acute bacterial meningitides, weakly positive in tuberculous meningitis and negative in lymphocytic choriomeningitis and the virus encephalitides.

The author also claims that this reaction can be used to differentiate cases of coronary occlusion

*Löfström, C.
logic and clinical
Preliminary studies
in the study of
1932, 1933.

from congestive failure without occlusion, since it is present only during the phase of coronary occlusion when tissue breakdown is taking place. Likewise he believes that the reaction may differentiate chronic endocarditis with valvular defects and subacute bacterial endocarditis, the capsular swelling being demonstrated in the latter but not in the former.

As a routine method for the clinic, the test for nonspecific capsular swelling has the great advantage that it is simple to perform and easy to evaluate. Should the author's claims be substantiated, the reaction may prove to be an extremely useful tool.

MEDICAL EPONYM

RIEDEL'S STRUMA

Professor Bernhard Moritz Karl Ludwig Riedel (1846-1916), of Jena, discussed the topic "Die chronische, zur Bildung eisenharter Tumoren führende Entzündung der Schilddrüse [Chronic Inflammation of the Thyroid Gland Leading to the Formation of Iron-hard Tumors]" at the twenty-fifth congress of the Deutsche Gesellschaft für Chirurgie, on May 30, 1896. His remarks are published in *Verhandlungen der deutschen Gesellschaft für Chirurgie* (1:101-105, 1896). A portion of the translation follows:

I present for your consideration a new, unusual property of the thyroid gland. . . .

There came under my care a forty-two-year-old man who for six months had noticed an increase in size of his thyroid gland, together with moderately severe dyspnea. There was a bilateral tumor, not very large, but extraordinarily hard and immovable. I supposed it to be a malignant goiter, and on November 30, 1883, attempted operation, exposed the tumor and saw at once that it was very firmly adherent to the carotid artery and the internal jugular vein on either side, resected a portion of the internal jugular, then after removal of a bit of the goiter about as large as a walnut, cut short the operation, since I was forced to consider the case inoperable. . . . Half a year later the man reported that he was entirely well and able to work. In the meantime we had studied the specimen and found in it no trace of any new-growth. It was an inflammatory process; infiltration with round cells was demonstrated; carcinoma and sarcoma were ruled out, and the patient had neither tuberculosis nor syphilis. . . .

Twelve years later a second case was encountered.

Inspection of the preparation gives no hint of the hardness of the growth; one would expect firm, fibrous tissue as a constituent of the tumor, but we see only masses of round cells, as described.

The growth seems even harder before operation: this is explained by the abundant firm adhesions of the tumor to the surrounding soft parts, especially with the blood vessels, nerves and trachea. . . .

It would seem . . . as though for the present only partial excision of the growth exerts an influence on the inflammatory process.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

EXECUTIVE COMMITTEE OF THE COUNCIL

On December 29, 1943, the Executive Committee of the Council, on the recommendation of the Committee on Membership and representatives from the supervising censors, took the following action:

Accepted the resignations of the following named fellows, under the provisions of Chapter I, Section 7, of the by-laws, these resignations to be effective as of January 1, 1944:

Medinger, Fred G. (nonresident), 326 South 19th Street, Philadelphia.

Strong, Seth L. (Plymouth), Marshfield Hills.

Reinstated the following named fellow, who had resigned from the Society while in good standing, under the provisions of Chapter I, Section 10, of the by-laws:

Houghton, Henry L. (Suffolk), 176 Commonwealth Avenue, Boston.

Allowed the following named fellow to change his membership from one district society to another, without change of legal residence, under the provisions of Chapter III, Section 3, of the by-laws:

Simmons, Fred A., 264 Beacon Street, Boston (Norfolk to Suffolk).

Remitted the dues, including those of 1941, 1942 and 1943, of the following named fellow who is ill and incapacitated, under the provisions of Chapter I, Section 6, of the by-laws:

Jones, Raymond C. (Worcester North), Ashby.

Reinstated following named fellows, under the provisions of Chapter I, Section 10, of the by-laws, who had been deprived of membership for the non-payment of dues, provided their arrears in dues at the time they were dropped plus the dues for 1944 be paid to the treasurer of the Society:

Karl'sberg, Isador J. (Middlesex South), 164 Main Street, Hudson. Joined 1932. Deprived 1939.

Parris, Roland O. (Barnstable), 18 Locust Street, Falmouth. Joined 1916. Deprived 1934.

Rifkin, A. (Plymouth), 197 Main Street, Brockton. Joined 1929. Deprived 1938.

The personnel of the Committee on Membership is as follows: Harlan F. Newton, *chairman*; John E. Fish; Peirce H. Leavitt; A. William Reggio; and Sumner H. Remick. The representatives of the supervising censors are as follows: William H. Allen; H. Quimby Gallupe; and Albert E. Parkhurst.

MICHAEL A. TIGHE, M.D., *Secretary*
Executive Committee

SECRETARY'S OFFICE

I believe that the following letter, recently received from Dr. Victor Johnson, secretary of the Council on Medical Education and Hospitals of the

American Medical Association, will be of interest to the members of the Society.

MICHAEL A. TIGHE, *Secretary*

December 23, 1943

Dr. Michael A. Tighe, Secretary
Massachusetts Medical Society
3 The Fenway
Boston, Massachusetts

Dear Doctor Tighe:

In the November 25 issue of the *New England Journal of Medicine* there appears, on pages 832, 833 and 834, a discussion of the relationships of the Society with the College of Medicine of Middlesex University. The letter from Dr. Stephen Rushmore is quoted in which the following statement is made:

There has been expressed a fear that hospitals approved by the Council on Medical Education of the American Medical Association would lose their status as hospitals. The Council on Medical Education of the American Medical Association would lose its status as a hospital if it were to be closed by the State.

It occurs to me that you might be interested in knowing the exact policy adopted by the Council on Medical Education and Hospitals of the American Medical Association with regard to students from schools not on its approved list being accepted by approved hospitals for clinical instruction. The policy of the Council is embodied in the following statement:

The interest of the Council on Medical Education and Hospitals of the American Medical Association in hospitals approved for the training of interns and residents is primarily in the maintenance of a satisfactory educational program for the training of house officers. In the case of hospitals which in addition to internships and residencies also offer training to undergraduate medical students, the Council is also

interested in instances where the hospital contemplates acceptance of students from more than one medical school.

Yours sincerely,

[Signed] Victor Johnson

VICTOR JOHNSON, M.D., *Secretary*

DEATHS

FLANAGAN—James E. Flanagan, M.D., of West Roxbury, has been reported missing as a result of the sinking of the destroyer *Turner*.

Dr. Flanagan received his degree from Tufts College Medical School in 1938. He had been practicing medicine about four years when he entered the Navy a year ago. He held the rank of lieutenant at the time of his death. He was a member of the Massachusetts Medical Society and the American Medical Association.

KERRIGAN—John J. Kerrigan, M.D., of Fall River, died January 6. He was in his sixty-sixth year.

Dr. Kerrigan received his degree from the College of Physicians and Surgeons, Baltimore, in 1906, and did post-graduate work abroad. For many years he was on the staff of the Massachusetts Eye and Ear Infirmary. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, a son and a daughter survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

NEW LAW REGARDING PROPHYLACTIC TREATMENT OF EYES OF INFANTS

Attention is directed to amended Chapter 111, Section 109A, of the General Laws, which requires physicians to record on the birth certificate the

prophylactic treatment of the eyes of the newly delivered child. This amendment became effective on June 2, 1943. Prior to that date the law required only that the physician or hospital officer treat the eyes of the newborn within two hours after birth with a department-approved prophylactic. The present law reads as follows:

The physician, or hospital medical officer registered under section nine of chapter one hundred and twelve, if any, personally attending the birth of a child shall treat his eyes within two hours after birth with a prophylactic remedy furnished or approved by the department, and he shall record on the birth certificate the use of such prophylactic. Whoever violates this section shall be punished by a fine of not more than one hundred dollars.

It is suggested that physicians use the left margin of the certificate to record the prophylactic used.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR DECEMBER, 1943

DISEASES	RESUME		
	DECEMBER 1943	DECEMBER 1942	SEVEN YEAR MEDIAN
Anterior poliomyelitis	15	2	1
Chicken pox	163	1444	1511
Diphtheria	44	12	18
Dog bite	431	505	561
Dysentery bacillary	30	6	16
German measles	118	190	63
Gonorrhea	477	286	335
Measles	1319	1871	1087
Meningitis meningococcal	65	27	7
Meningitis other forms	16	10	4
Meningitis undetermined	4	0	0
Mumps	671	1080	597
Pneumonia lobar	576	327	407
Salmonella infections	4	7	4
Scarlet fever	978	1307	751
Syphilis	560	489	444
Tuberculosis pulmonary	214	239	241
Tuberculosis other forms	18	13	26
Typhoid fever	3	4	5
Undulant fever	3	2	3
Whooping cough	343	1171	828

*Pfeiffer bacillus meningitis only other form reportable previous to 1941

COMMENTS

Anterior poliomyelitis has shown the usual seasonal decline since the peak of 121 cases in September, but nonetheless the December level was fifteen times the seven year median. Diphtheria on the other hand, has been showing a steady rise since September, reaching a point nearly two and a half times the seven year median. The December prevalence has not been as high since 1935. The number of cases of lobar pneumonia was also high compared to that reported in December in recent years.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from Boston, 1, Fall River, 1, Haverhill, 2, Lynn, 1, Newton, 2, North Adams, 1, Norwood, 1, Peabody, 1, South Hadley, 1, Waltham, 3, Winchester, 1, total, 15.

Anthrax was reported from Salem, 1, total, 1. Diphtheria was reported from Amesbury, 1, Barre, 1, Bedford, 1, Boston, 16, Cambridge, 1, Hopedale, 1, Medford, 1, Melrose, 1, New Bedford, 1, Salem, 1, Saugus, 1, Somerville, 11, Taunton, 6, Watertown, 1, total, 44.

Dysentery, bacillary, was reported from Adams, 1, Boston, 5, Cambridge, 1, Haverhill, 4, Lowell, 1, Worcester, 18, total, 30.

Encephalitis, infectious, was reported from East Longmeadow, 1, Holyoke, 1, Lowell, 1, Springfield, 1, Worcester, 1, total, 5.

Malana was reported from Fort Devens, 8, Haverhill, 1, Worcester, 2, total, 11.

Meningitis meningococcal, was reported from Barnstable, 1, Boston, 25, Bourne, 1, Cambridge, 2, Camp Edwards, 4, Canton, 1, Chelsea Naval Hospital, 1, Cohasset, 1, Danvers, 1, Dedham, 1, Everett, 2, Fairhaven, 1, Fall River, 1, Fort Devens, 2, Framingham, 1, Gloucester, 1, Greenfield, 1; Hingham, 1, Holyoke, 1, Lawrence, 1, Lowell, 1, Milton, 1;

New Bedford, 1; North Adams, 1; Plymouth, 2; Salem, 2; Springfield, 3; Westwood, 1; Weymouth, 1; Winthrop, 1; Worcester, 1; total, 65.

Meningitis, Pfeiffer-bacillus, was reported from: Boston, 1; Lynn, 1; Springfield, 2; total, 4.

Meningitis, pneumococcal, was reported from: Fall River, 1; Marblehead, 1; Medford, 1; Oxford, 1; Worcester, 1; total, 5.

Meningitis, staphylococcal, was reported from: Fall River, 1; total, 1.

Meningitis, streptococcal, was reported from: Marlboro, 1; Springfield, 1; total, 2.

Meningitis, other forms, was reported from: Boston, 3; Methuen, 1; total, 4.

Meningitis, undetermined, was reported from: Arlington, 1; Fort Devens, 1; Springfield, 1; Worcester, 1; total, 4.

Salmonella infections were reported from: Andover, 1; Boston, 1; Haverhill, 1; Northfield, 1; total, 4.

Septic sore throat was reported from: Amesbury, 1; Boston, 13; Cambridge, 1; Lawrence, 2; Medford, 1; Milton, 1; total, 19.

Tetanus was reported from: Fall River, 1; Raynham, 1; total, 2.

Trachoma was reported from: Medway, 1; total, 1.

Typhoid fever was reported from: Boston, 1; Medford, 1; total, 2.

Undulant fever was reported from: Adams, 1; Great Barrington, 1; Hatfield, 1; total, 3.

CORRESPONDENCE

WAGNER-MURRAY-DINGELL BILL

To the Editor: It did not seem to me quite fair that the letter under date of December 2, 1943, signed by the president and secretary of the Massachusetts Medical Society should have been sent to our representatives in Congress, because as I read the letter it implies that the Society has already expressed an opinion on the subject matter involved. This I am informed is not the case.

I know an appreciable number of members of the Society who do not believe in the sentiments expressed in this letter, and therefore, irrespective of what the Council will decide in February, it seems to me only fair to inform the members from Massachusetts in Congress that a minority at least of the Massachusetts Medical Society have a different point of view. I am, therefore, sending to the Massachusetts representatives in Congress a letter, a copy of which I am enclosing.

I have always hoped that the *Journal* would be willing to present both sides of a controversial matter, so I hope that you will be willing to publish this letter with the enclosure.

CHANNING FROTHINGHAM, M.D.

1153 Centre Street

Jamaica Plain, Massachusetts

* * *

Dear Sir:

January 12, 1944

In the December 2, 1943, issue of the *New England Journal of Medicine*, on page 884, there appears a letter signed by the President and Secretary of the Massachusetts Medical Society which was sent to Massachusetts members of the Senate and the House of Representatives in Congress. This letter gives the impression that the statements expressed therein are the sentiments of the Massachusetts Medical Society. Up to the present time neither the Society nor its Council, which often expresses opinions for the Society, has taken any formal action on the merits of the Wagner-Murray-Dingell Bill. What the action of the Council of the Massachusetts Medical Society or the Society itself will eventually be in regard to the Wagner-Murray-Dingell Bill remains for the future to decide. In the meantime I would like to call your attention to the fact that there are many members of the Massachusetts Medical Society who are not in sympathy with the statements expressed in this letter of December 2, 1943, referred to above and who believe that there is a possibility to accomplish a tremendous improvement in the delivery of medical care to the citizens of Massachusetts by developing a program along the general lines outlined in the Wagner-Murray-Dingell Bill.

A group of doctors with whom I am connected has made a careful study of the medical aspects of Senate Bill 1161 and has offered constructive criticism in regard to the Bill. I am enclosing a copy of the statement of this group thinking that it might be of interest to you.

Sincerely yours,

CHANNING FROTHINGHAM, M.D.

President of the Massachusetts Medical Society (1937-1939)

BOOK REVIEWS

Doctors Aweigh: The story of the United States Navy Medical Corps in action. By Rear Admiral Charles M. Oman (MC) U. S. N. 8°, cloth, 231 pp., with 10 illustrations. Garden City, New York: Doubleday, Doran and Company, Incorporated, 1943. \$2.50.

The subtitle gives the key to this clear-cut, well-written story of forty years' experience in the United States Navy. The author has seen plenty of action, and he knows how to report it. Here is the story of the preparedness and efficiency of the Navy Medical Corps at Pearl Harbor on that peaceful sunny morning of December 7, 1941, which will thrill and please any doctor. Again one may read of the astounding adventures of Dr. Wassell and of Dr. White on the *Lexington* and the story of the brilliant appendectomy performed by Pharmacist's Mate Lipes while the submarine to which he was attached rested on the bottom of the Pacific. These and many other tales, along with good advice, make sound reading and leave one proud and grateful for the high standards of the United States Navy and the splendid men who maintain them.

Pictorial Handbook of Fracture Treatment. By Edward I. Compere, M.D., and Sam W. Banks, M.D. 8°, cloth, 35 pp., with 171 illustrations. Chicago: The Year Book Publishers, Incorporated, 1943. \$4.25.

Recent advances in the management of fractures have resulted in the introduction of so many new methods that the general practitioner, who in most cases must be the one to institute the first treatment to which a fracture victim is subjected, should be acquainted with those procedures that have been shown to have been attended with the most gratifying results.

This small volume of Compere and Banks presents in compact and well-illustrated text a discussion of the essentials for diagnosis and treatment. The basic facts concerning repair in bone, — based on knowledge of the pathology of fractures, — the rate of healing, and causes of delayed union, together with a clear presentation of methods of reduction, the principles of aftercare and the complications that sometimes follow, are included in the first part of the book. The four remaining sections are devoted to the upper and lower extremities, the trunk, the face and the skull. Dislocations are also included. Many line drawings and photographs of x-ray films are used to illustrate the various types of fracture and their reduction and fixation by measures that have proved satisfactory.

Both the authors and publishers have acquitted themselves most creditably, and the practicing physicians have at their service a most helpful guide to their efforts.

Diseases and Injuries of the Larynx: A textbook for student and practitioners. By Chevalier Jackson, M.D., Sc.D., LL.D., and Chevalier L. Jackson, M.D., M. Sc. Second edition 8°, cloth, 633 pp., with 197 illustrations. New York: The Macmillan Company, 1942. \$8.00.

This is a new edition of a textbook that has become a classic in the short time since the appearance of the original edition in 1937. Surgeons within and outside the specialty are by now familiar with it, and many general practitioners have found it to be their best adviser in borderline cases. The style is most vivid and personal, and when reading the book, one is subject to the sensation of being present at one of the widely known courses of the authors.

There are 11 color plates, more than 100 halftones and 22 pen and pencil drawings to clarify the clinical picture. The new chapter on war surgery is an important and timely addition. Incidence, etiology, special pathology and accessory injuries in war are discussed, together with their peculiar symptoms and the treatment and prognosis; next, the authors consider organization for care of the wounded, chemical warfare by asphyxiating, irritating and poisonous gases and smoke and, finally, the psychical laryngeal traumas of war.

In its new form, the textbook will without doubt continue to speak *viva voce* to any member of the profession who turns to it with his medical or surgical problems regarding the larynx.

(Notices on page xiii)

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PATHOLOGY, CLINICAL MANIFESTATIONS AND TREATMENT OF LESIONS OF THE INTERVERTEBRAL DISKS*

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LACONIA, NEW HAMPSHIRE

LESIONS of the intervertebral disks are extremely common, but do not induce clinical manifestations in every case. If present, clinical signs and symptoms are sometimes almost indistinguishable from those caused by diseases of the viscera, joints, muscles and other parts. In many cases, therefore, it is difficult to decide whether the symptoms should be attributed to a disk lesion or to some other cause. Accordingly there is a divergence of opinion about the clinical significance and appropriate treatment of these lesions. Some surgeons ascribe many and different symptoms to certain lesions of the disk; others tend to discount the same lesions as incidental abnormalities. Such a discrepancy seems to demand a reinvestigation of the problem by means of statistical methods.

On the basis of 826 cases of disk lesions observed during the last eight years, of a control series of 200 persons without symptoms, and of another control series of 100 persons with complaints suggestive of disk lesions, an attempt has been made to ascertain whether correlations can be established between the clinical and the anatomical findings, and whether principles can be defined by which treatment may be directed.

PATHOLOGY

The common disk lesions seem to fall into two main groups, those caused by rupture and those due to degeneration. As a result of trauma or strain, a piece of cartilage may be detached from a normal disk,¹ or the nucleus pulposus may be squeezed out of the disk center.^{2,3} The displaced material may be pressed beyond the disk margin, either through the fibers of the longitudinal ligaments — for example, backwards into the spinal canal, where it may encroach on the cord^{4,5} — or vertically, into an

adjacent vertebral body, through congenital defects⁶ or traumatic fissures⁷ of the osseous and cartilaginous surfaces. It appears that forward and backward displacement occurs when the disk is less resistant than the bone, and that intrusion of disk material into the vertebrae implies that the bone is less resistant than the disk; but the two modes of displacement may combine.

With advancing years many disks normally lose in turgor and volume and grow flat and inelastic as a result of dehydration and increase of fibers of the disk cartilage.⁸ These morphologic alterations are probably signs of a change of the colloidal phase of the connective tissue. They are believed to be caused by the innumerable unnoticed injuries of daily life.⁷ In some persons this wear and tear seems to cause a premature aging or degeneration, especially of those disks that are located in the most movable vertebral regions — that is, the lower cervical and lower lumbar segments.^{9,10}

In addition to this quasi-spontaneous degeneration, fibrosis and flattening may develop as a result of disk rupture and of diseases of vertebral bone. Rupture of the disk, both into the vertebral body and through the longitudinal ligaments, often sets up a reaction marked by increasing fibrosis of the disk cartilage, indistinguishable histologically from involutionary degeneration.^{3,6} Bone disease may involve the disks either directly or indirectly. Infection of the vertebral body may spread directly into them through the sievelike lamina cribrosa; although resistant against most infections,³ a disk, once infected, deteriorates rapidly,¹¹ and residual disk cartilage may undergo degeneration. But even when it escapes infection, a disk adjacent to an infected vertebral body usually grows thin and fibrous in the course of several months or years (Fig. 1), although the bone infection itself may have become arrested in the meantime. Since the disk, which is normally avascular during adult life,⁶ receives its nutrition from the vertebral body,⁷ it is conceivable that degeneration occurs in these cases because nu-

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trition was inadequate or faulty during the period of bone infection.

It should be recalled at this point that nothing in the pathology of the disk differs from the pathology of cartilage in general. The nucleus pulposus, the

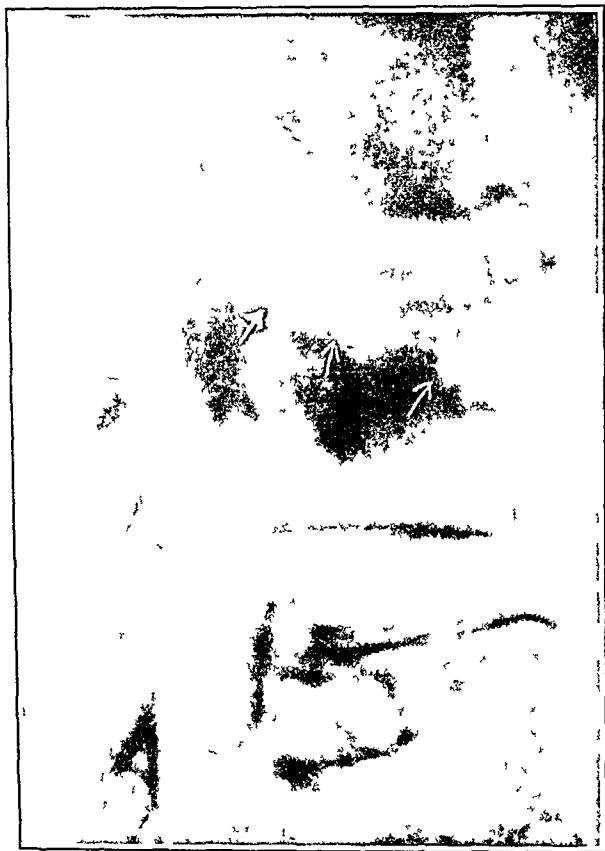


FIGURE 1. Flattening of the Intervertebral Disk as a Result of Infection of a Vertebral Body.

The arrows point to small areas of rarefaction in the fourth lumbar vertebral body. The superjacent intervertebral space is about half the width of the normal subjacent interspace, owing to flattening of the disk. The patient, a forty-two-year-old man, developed sudden pain in the back during recovery from a blood-stream infection due to *Staphylococcus aureus*.

presence of which somewhat complicates the picture, is an inert part that, although derived from primitive connective tissue, has no more life of its own than, for instance, the synovial fluid; it plays no active part in determining the morbid processes observed. Cartilage is a connective tissue which the omnipotent mesenchymal cell fails to regenerate effectively. It may either undergo necrosis in its various forms and phases or be invaded and replaced by vascular connective tissue. Although small scattered areas of newly formed cartilage may be produced, this repair is hardly ever sufficient to restore the original volume and resiliency of injured cartilage. Lesions of the disk exemplify this rule. The injured parts of a disk grow flat, less elastic and more fibrous, no matter what were the cause and nature of the

original injury.³ As the disk thins down, the vertebrae at this level approach each other. As a result the following changes may take place.

Marginal osteophytes (hypertrophic spondylitis). As the bufferlike action of the disk diminishes, the horizontal vertebral surfaces sustain increased static stress and the edges of the vertebral bodies may come into contact during certain movements. This slight but continual trauma may cause minute fractures,⁶ which normally¹² heal with callus formations. The fractures recur, and the callus formations grow, especially into the free space between the vertebral margin and the longitudinal ligaments,¹³ thereby forming the marginal overgrowths (Fig. 2) that resemble exostoses of peripheral joints and are therefore commonly designated as osteoarthritis of the spine. According to its definition, however, osteoarthritis is a disease of the synovial joints and is marked by the wearing off of free articular cartilages. The joint formed by the disk and vertebrae has no free cartilages; it is not a synovial joint but a synchondrosis, which has been named the "vertebral symphysis."¹⁴ Hence marginal osteophytes at the level of flattened disks do not fit the anatomical definition of arthritis; and since it has been shown that they are not associated with the clinical symptoms of arthritis,¹⁴ these osteophytes should not be grouped with arthritis.

Osteoarthritis of the apophyseal joints (hypertrophic spondylarthritis). At the level of a thinned disk the articular processes are crowded together, and their articular surfaces, or facets, become displaced, usually with the superjacent facet sliding backward and downward along the subjacent facet (Fig. 3).^{15, 16} This often causes straining of the surrounding capsules of the apophyseal joints and the ligaments and may produce a gradual wearing off of the articular cartilages that are affixed to the facets¹² — a lesion that corresponds in every respect to osteoarthritis of the peripheral joints and is a true arthritis of the spine. As in osteoarthritis of the peripheral joints, eburnation, ecchondroses and exostoses may, but need not, develop along the articular surfaces involved. This hypertrophic spondylarthritis occurs in less than 20 per cent of all cases of disk thinning; in the majority of cases the cartilages of the apophyseal joints seem to resist the strain successfully.¹²

Bony impingement. The displacement of articular processes may amount to impingement of the tip of the subjacent facet on the base of the superjacent facet.¹⁵⁻¹⁷ The impinging tip may produce in the opposing base an erosion resembling a drill hole, with subsequent reactive eburnation of the surrounding bone. This was noted in 2.8 per cent of this series.

Contact between spinous processes. When the disk thins down, contiguous spinous processes may come into contact and form eburnation and osteophytes like the margins of the vertebral bodies.¹⁸ This was recorded in 0.6 per cent of this series.

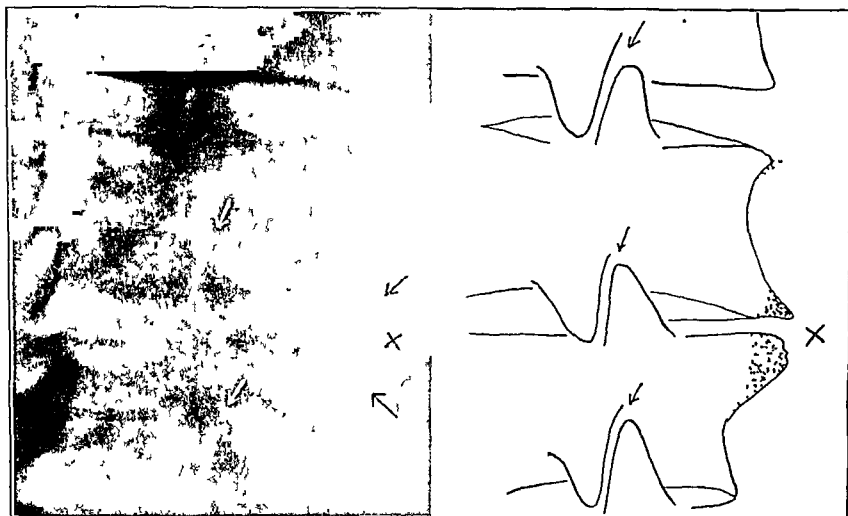


FIGURE 2 Secondary Osteophytic Changes in the Vertebral Bone and Joints as a Result of Disk Thinning

The fourth lumbar intervertebral space is less than half the width of the other interspaces owing to flattening of its disk (x). Osteophytes have formed at the central margins of the vertebral bodies (black arrows), but the apophyseal joints have remained normal (white arrows). On the tracing the stippled areas correspond to the secondary lesions. The patient, a forty-one year old woman, complained of sciatic pain, there was no backache.

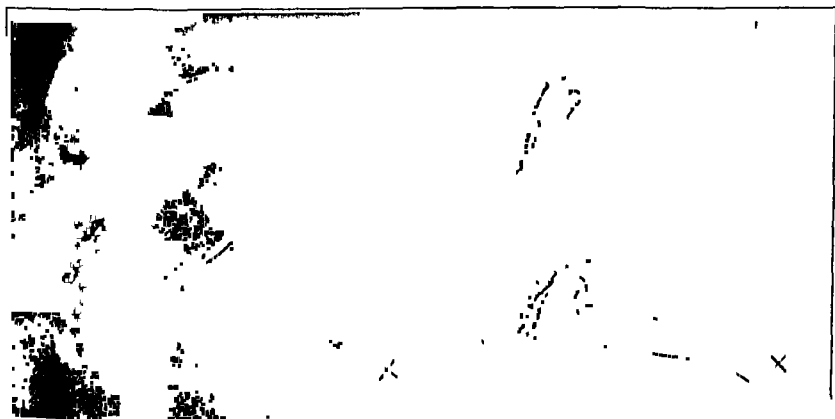


FIGURE 3 Secondary Spondylarthritic Changes in the Vertebral Bone and Joints as a Result of Disk Thinning.

The fourth lumbar intervertebral disk is flattened (x). The facets at this level are ragged and eburnated, and the intervening apophyseal joint space is narrowed (white arrows). This is a diskogenetic spondylarthrosis. On the tracing the stippled areas correspond to the secondary lesions. The patient, a forty-seven-year old man, complained of severe pain in the lower back, the movements of the lumbar spine were severely restricted.

Narrowing of the neural foramen At the level of a thinned disk the neural foramen grows narrow.^{13, 17, 19-20} The nerve root that passes through it may become compressed.¹⁶ Marginal osteophytes

arising from the posterior margins of the vertebral bodies²¹ and from the tips of the articular processes,¹⁷ as well as ossification of the yellow and intra-articular ligaments¹⁷ and swelling of the apophyseal

joint capsule,¹² may add to the compression. The most frequent sites of pressure on nerve roots are the lower cervical and lower lumbar segments, not only because disk thinning is commonest in these regions,^{9, 10} but chiefly because the nerve roots are thicker and the foramens not proportionally wider than in other vertebral sections. Since the caliber of the nerve root, the original width of the foramen and the amount of narrowing vary from case to case,^{14, 23} compression of nerve roots does not occur in every case of disk thinning. Narrowing of neural foramens was present in 92 per cent of the cases of disk thinning in this series.

Bulging of disks into the spinal canal. A softened, fibrosed or thinned disk may, under the pressure of superincumbent parts, be flattened out so that it protrudes beyond the vertebral edges. Since the longitudinal ligaments at the level of a flattened disk grow loose,¹³ they yield and bulge sideward, together with the disk. The protruding parts may cause pressure on the spinal cord.²⁴

The secondary changes above enumerated have been designated as "diskogenetic," in order to imply that they are all caused by the disk lesion. One may speak of diskogenetic osteophytes, diskogenetic spondylarthritis and so forth, in order to distinguish these lesions from similar alterations that are due to some other cause. Marginal osteophytes, for instance, may be present at the level of perfectly normal disks, especially as a result of low-grade bone infection, and osteoarthritis of the apophyseal joints may be produced by several different factors.^{12, 14} The clinical manifestations associated with disk lesions have been named "the diskogenetic syndrome," and the totality of anatomical and clinical findings has been termed "diskogenetic disease."¹⁰

CLINICAL MANIFESTATIONS

Not every disk lesion produces clinical manifestations. In a series of 200 apparently healthy persons not conscious of any symptoms, flattened disks were found in 22 cases (11 per cent). Conversely, in a series of 312 unselected cases of disk thinning, clinical signs and symptoms pointing to a lesion of the involved vertebral segments were present, or had been present at different periods, in 267 cases (85 per cent). These figures dovetail with a sufficient degree of accuracy, but are not necessarily representative. In many cases the symptoms are transient or recurrent rather than persistent; and when a patient happens to be free of pain and discomfort at the time of the x-ray examination, he is classified with the "silent" group, although he may develop symptoms in the future, or may have forgotten about symptoms that he had in the past. One often hears patients state that they never had any pain or disability until they are reminded by a companion of the "sciatica," "rheumatism" or "sore shoulder," for which they consulted physicians and osteopaths in previous years.¹²

The main difficulty in evaluating the clinical significance of disk lesions consists in the fact that signs and symptoms virtually identical with those caused by diseases of the disk may be the result of involvement of viscera, muscles, bursas, peripheral joints, spinal cord, and peripheral nerves. In a series of 100 patients complaining of symptoms suggestive of lesions of the cervical disks, flattening of the disks was demonstrable in 89 cases (89 per cent); in 34 of these, 11 showed evidence of bursitis, 5 of acromioclavicular arthritis, 2 of tuberculosis of the shoulder, and 17 of aortic sclerosis, coronary disease and cardiac failure. In the remaining 11 cases, myalgia, polyneuritis and subdeltoid bursitis were present in the absence of disk lesions in 8 patients, and the source of the complaint could not be ascertained in 3 cases. This shows that clinical manifestations suggestive of disk lesions are due to some other diseases in about 10 per cent of the cases, and that their connection with a demonstrable disk lesion is questionable in at least another third.

From these observations it should be inferred that the roentgenographic demonstration of a diseased disk does not prove the diskogenetic origin of the complaint. This limitation was perhaps not sufficiently emphasized in early reports, including mine.^{17, 25} On the other hand, the figures indicate that in about two thirds of the cases, certain clinical manifestations are in all probability due to the disk lesions disclosed on roentgenograms.

Axiomatic notions have obscured the problem. For instance, some authors^{23, 24, 26} maintain that narrowing of a neural foramen cannot amount to compression of the nerve root by the surrounding bone. Anatomic specimens showing such a compression were presented by Hadley¹⁶ in 1938. In the same year, unquestionable clinical evidence of damage to nerve roots passing through narrowed neural foramens was submitted.²³ The signs and symptoms noted in these patients were found to reappear in those cases in which examination suggested, but did not prove beyond doubt that the clinical manifestations were actually caused by the disk lesions present. These manifestations were as follows:

Pain in the back or neck at the level of the involved disk. This is not common; it was noted in 21 per cent of this series; its incidence varied with the vertebral region involved.

Limitation of vertebral movements at the level of the involved disks. This was recorded in 18 per cent of the series and varied with the localization of the disk lesion.

Manifestations of radicular neuralgia or neuritis. These are multifarious, consisting of pain in the peripheral region that corresponds to the involved nerve segment, weakness and atrophy of muscles, hyperesthesia, paresthesia and anesthesia, and trophic changes of the skin

muscle and bones. Manifestations of radicular neuralgia and neuritis were present in 72 per cent of the series.

CORRELATIONS BETWEEN CLINICAL AND ANATOMICAL FINDINGS

A study of the correlations between the clinical and anatomical findings above classified seems to show that the clinical manifestations of disk lesions vary with a number of factors.

Vertebral region involved. Flattening of cervical disk was associated with pain in the neck in 4 per cent of the cases; with limited motion of the cervical spine in 11 per cent; and with recurrent pain in the shoulders, forearm, precordium and fingers in 72 per cent. In the presence of flattened thoracic disks pain in the back was noted in 29 per cent of the patients; limited motion of the thoracic spine could not be determined, since the movements of this region are normally very scant; and persistent or recurrent intercostal neuralgia, occasionally accompanied by recurrent herpes zoster, was present in 36 per cent of the cases. Of the patients with flattened lumbar and lumbosacral disks, 37 per cent complained of pain in the low back, 31 per cent of limited motion in this region, and 49 per cent of recurrent sciatic pain.

Thinning of disks. The incidence and severity of the clinical manifestations were not proportional to the degree of disk thinning, as measured by the width of the intervertebral space. No correlation could be established between any of the clinical signs and symptoms, on the one hand, and the degree of disk thinning, on the other.

Involvement of other vertebral parts. The presence, amount and size of osteophytes at the anterior margins of the vertebral bodies did not seem to determine the incidence, kind and severity of the clinical manifestations. All things being equal, the signs and symptoms were the same in patients with and those without osteophytes. Osteophytes at the posterior margins of the vertebral bodies seemed to accentuate and maintain radicular nerve pain; all things being equal, the incidence of radicular neuralgia was 43 per cent higher in the presence than in the absence of these exostoses.

Bony impingement of articular processes was associated with persistent backache and with limitation of vertebral motion in all the cases; no case of bony impingement without definite clinical symptoms was encountered. Radicular pain was present in 69 per cent of these patients. In 89 per cent of the patients with diskogenetic involvement of the apophyseal joints (hypertrophic spondylarthritides), pain and diminished mobility of the involved vertebral region were noted, often associated with tenderness on pressure (Fig. 4). Conversely, only 8 per cent of all patients with thinned disks but without involvement of the apophyseal joints were

conscious of pain, discomfort or stiffness of the involved parts of the spine (Fig. 5). Contact between spinous processes did not seem to alter or accentuate the symptoms present and was noted in an equal number of patients who were free of symptoms. The cases of bulging of a degenerated disk into the spinal canal were not numerous enough to warrant statistical evaluation.

These observations indicate that the clinical manifestations of disk lesions are determined, at least to some extent, by two main factors: the vertebral region involved, and the condition of the apophyseal joints. Lesions of cervical disks rarely cause any symptoms in the neck itself, but lesions of the lumbar and lumbosacral disks cause low-back pain and limitations of movements in about one third of the cases. On the other hand, lesions of cervical disks induce radicular manifestations in a majority of cases, and lesions of the lumbar and lumbosacral disks cause radicular neuralgia in only about one half of the cases. Lesions of the thoracic disks seem to remain clinically silent in about two thirds of the patients. Pain and limited motion in the spine seem to develop chiefly when the apophyseal joints have become involved, irrespective of the seat of the lesion.

On the negative side stand two findings that, although conspicuous, do not seem to play a part in determining the clinical manifestations in most cases. These are osteophytes of the vertebral margins — so-called "osteo-arthritis of the spine" — and the amount of disk thinning. Marginal osteophytes, no matter how large and numerous, do not cause symptoms unless they arise at the posterior vertebral edges and project into the neural foramina. These posterior osteophytes occur not infrequently in the cervical spine,^{13, 17, 22, 23} but are rare in the lumbar region and usually absent in the thoracic vertebrae; they are difficult to recognize on routine radiograms and are usually overlooked. The only influence that osteophytes of the anterior vertebral edges seem to have, according to my observations, is that they may limit anterior flexion of the spine when they are bulky; but the patients are rarely conscious of this limitation, even when it can be definitely shown on roentgenograms made during movements of the spine. Finally, the amount of disk thinning did not seem to be responsible for the incidence and severity of clinical manifestations in this series. In many patients who were free of symptoms complete obliteration of the intervertebral spaces was present, whereas in others severe radicular neuralgia seemed to be caused by only moderate thinning of disks.

These observations confirm the contention previously made — namely, that lesions of the disks cause symptoms felt in the periphery rather than in the spine, and that, in the presence of disease of the spine, pain and rigidity of vertebral regions are caused in most cases by involvement of the apophyseal

eal joints. Since disk lesions induce arthritis of the apophyseal joints in only about one fifth of the cases, symptoms felt in the spine are not common,

said to resemble toothache in the shoulder, wrist or gluteal region or in sciatic distribution is the commonest complaint for which medical advice is

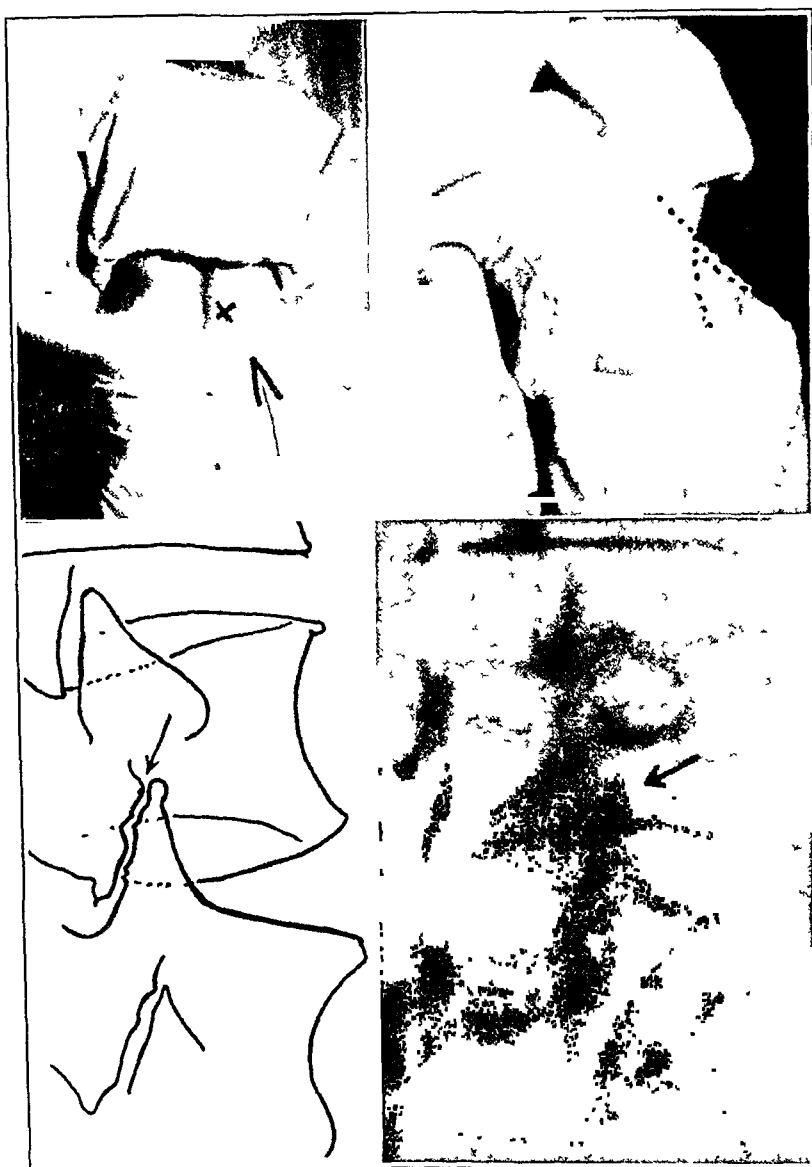


FIGURE 4. Result of Disk Thinning with Involvement of Apophyseal Joints.

The fourth lumbar interspace is narrowed, and the apophyseal joint at this level has ragged facets and a narrowed articular space (arrow, right lower corner). Compare with normal superjacent apophyseal joint. The patient, a thirty-six-year-old woman, had severe persistent pain in the back, with tenderness on pressure (x, left upper corner), impaired forward flexion (right upper corner) and no sciatic pain.

and the vertebral origin of peripheral pain easily escapes recognition.

CLINICAL COURSE OF DISKOGENETIC DISEASE

On the basis of the data above reported, and taking into account the experience with other patients not included in this series, one may draw a composite picture of the usual course of diskogenetic disease.

Early stage. Rarely before the age of thirty, and usually after the age of forty-five, recurrent pain

sought by these patients. The pain tends to be severer in the early morning, when it may awake the patients, and subsides in the course of the day to reappear in the evening. There is rarely pain in the back or neck at this stage, but a sensation of moderate stiffness may be present; it is often compared by patients to the muscle soreness that follows unwonted exercise. The symptoms may subside gradually without treatment in the course of about two years and need not recur. A history of a trauma incurred many years previously, such as a fall from

a horse, a diving accident and so forth, is obtained in many cases

Moderately advanced stage The pain in the extremities, shoulder and gluteal region becomes more pronounced, and the intervals of relative or complete relief grow shorter. The movements of the painful shoulder or leg are definitely limited apparently as a result of muscular defense. Sensory disturbances, such as numbness and tingling of the fingertips and of the soles, set in, and so-called 'electric' sensations in the arm or leg may wake the patients

the floor are some of the movements that cannot be carried out. Trophic changes, such as herpes zoster (Fig 6), may occur. Atrophy of the skin, especially in the region proximal to the nails, may develop, and the phalangeal bones may become rarefied.³ In many cases the reaction of degeneration is positive. Finally a peculiar resilient swelling of the wrist, fingers or foot may develop, and the involved limb becomes completely disabled (Fig 7). At this stage, spontaneous improvement does not occur, and the hand or foot becomes crippled if not treated



FIGURE 5 Result of Disk Thinning with Involvement of Apophyseal Joints

The fourth lumbar interspace is narrowed (arrows left upper corner) but the apophyseal joints at this level are normal (ulster arrows right upper corner). This patient had severe sciatica with trophic edema of the right foot (arrow right lower corner) with perfect mobility of the lumbar spine

with a sudden shock at night. The grip of the hand may become weak, and the involved leg feels heavy. Usually some degree of atrophy of the deltoid, biceps, interosseous and thenar muscles, or of the corresponding muscles of the leg, is noted. Spontaneous recovery at this stage seems to be exceptional.

Advanced stage As the disease progresses, the pain becomes persistent and muscular atrophy becomes definite. Pain in the low back and neck may be superadded. The movements of the involved limb are definitely limited owing to weakness of the muscles. Carving meat, fastening a dress on the back, tipping the hat and lifting an object from

Secondary deviations of the bones produce an appearance suggesting a severe deforming arthritis, but the joints are not involved and passive mobility is preserved. From these manifestations the symptoms of rupture of the disk into the spinal canal differ in the acute onset and persistence, but not in kind and severity. Such signs as back pain induced by sneezing and coughing are certainly not typical of disk rupture and may be observed in the presence of various other lesions of the vertebrae.

CONTRIBUTING FACTORS

In this series there were as many men as women patients with symptoms referable to disk lesions.

The highest incidence of diskogenetic symptoms in women was found in the age group of sixty to seventy years, but in men in the fifty-to-sixty-year group. Weight, height and general build did not seem to play significant parts. There were short, tall, stocky and slender people with the same symptoms, but symptoms seemed to appear at a younger age in stocky than in slender patients. Occupational and social factors could not be ascertained as contributing causes.

In 74 per cent of the patients, the diskogenetic symptoms were preceded by an infection, such as sore throat, sinusitis or cystopyelitis, and the com-

to the infection becomes manifest as a result of infection, and that infection precipitates the appearance of clinical symptoms. The influence of mental factors is difficult to determine.

TREATMENT

Reasonably complete follow-up records are available in 322 cases. The patients treated were observed during periods varying between eight months and seven years. Most of them were examined at intervals of eight to ten months.

An injured disk cannot be repaired; the fibrous tissue produced cannot be reversed into cartilage.

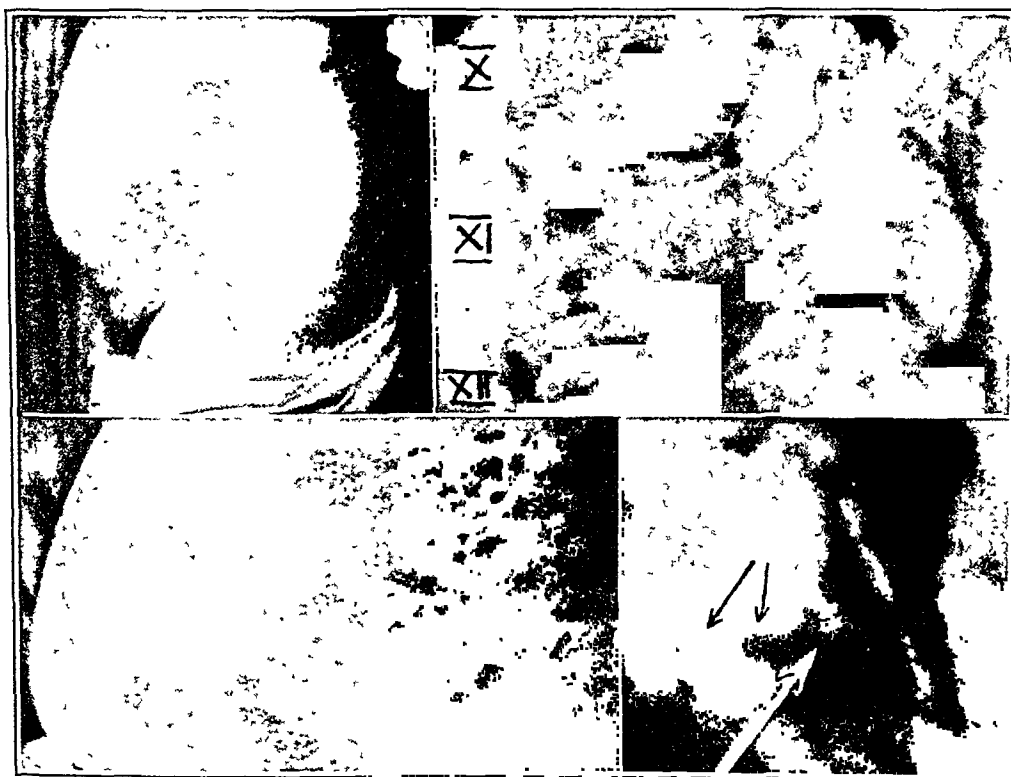


FIGURE 6. *Persistent Herpes Zoster as a Result of Diskogenetic Narrowing of Neural Foramens with Radicular Neuritis.*

The neural foramen between the eleventh and twelfth thoracic vertebrae is narrowed, and arthritic deformities encroach upon it (black arrows, right lower corner). There was a herpes zoster in the corresponding skin areas, persisting for a period of seven years. The pictures of the lower row were taken twenty-one months after those of the upper row. The patient was a sixty-three-year-old man.

plaint persisted after the infection had subsided. One may speculate whether this can be explained on the basis of a disturbed vitamin B metabolism. It is known that in the presence of most infections the vitamin B reserve is diminished, especially in the liver. It is conceivable that this deficiency affects first or foremost those nerve segments that have already sustained some damage as a result of compression in narrowed neural foramens. If infection alone were responsible for neuralgia in these cases, one would expect other nerve segments also to become involved. One may perhaps say that a localized nerve injury that was clinically silent previous

Most of the clinical manifestations, however, are caused not by the disk lesion itself but by the secondary alterations in the neural foramens and apophyseal joints resulting from the constriction of the intervertebral space. Rupture of the disk into the spinal canal is not always an exception to this rule; as will be shown, some of the symptoms associated with disk rupture may be caused by the associated disk thinning. If the narrowed intervertebral space could be widened permanently, no other treatment would perhaps be necessary, but this has not yet been achieved. Spinal fusion and grafting does not help to hold the vertebrae permanently a

normal distance, since in the course of a few years the fused or grafted osseous parts yield to the stress exerted by superincumbent parts. Treatment, therefore, still remains confined to attempts at controlling and eliminating pressure on the cord, radicular neuritis and manifestations of spondylarthritis. Although from the academic point of view this does not appear to be satisfactory, it often brings about considerable relief from, and sometimes complete disappearance of, pain and disability in this group of patients.

The surgical treatment of rupture of the disk into the spinal canal has been exhaustively discussed in the literature.^{5, 9, 27, 28} The scientific achievement

intervertebral space grew progressively narrow in the course of three or four years in spite of spinal fusion, probably because the ruptured disk degenerated and became flat, as set forth above. The recurrence of symptoms was probably produced by compression of nerve roots within the foramens.

In spite of these observations, the definite value of surgery should not be minimized, but perhaps sufficient time has not yet elapsed to judge on the long-range results of this operation.

Conservative treatment^{30, 31} consists in attempts at preventing further damage to the disks, in eliminating contributing factors and in control of pain.



FIGURE 7. Atrophy and Deformity of the Right Hand as a Result of Diskogenetic Radicular Neuritis. The disks below the fourth and sixth cervical vertebral bodies are flat, and the neural foramens at these levels are narrowed (arrows). The interosseous muscles of the right hand are severely atrophic, and the fingers are claw-like. Mobility of neck was perfect. The patient, a fifty-eight-year-old man had had recurrent pain in the right shoulder for about six years. One year became swollen and very painful. The swelling subsided, but he had any pain or stiffness of the neck. The case illustrates the manifestations.

and practical value of this procedure are untested, but there seems to be no complete agreement on the indications for operation. On the one hand, the fact that a patient consults a doctor because of persistent backache and sciatic pain has been considered a sufficiently valid reason for operation, on the other hand, it has been repeatedly shown that numerous lesions may produce the same clinical manifestations and roentgenographic appearance as does a ruptured disk.²⁹

Of 10 patients operated on by leading surgeons five years ago and earlier, 4 are still free of symptoms, but the clinical manifestations recurred in 6 patients, of whom 2 are now almost completely incapacitated. The failures in this series were due to two main causes. In 2 cases the symptoms were not caused by the rupture alone, but in part by the associated compression of nerve roots in the neural foramens and the displacement of the facets. Although compression of the cord was relieved by the operation, pressure on the roots in the foramens seemed to persist. In the 4 other cases the involved

Jarring of the spine can be prevented to some extent by wearing rubber heels and soles, refraining from lifting heavy objects and bending at the hip and knee joints instead of stooping when reaching for an object on the floor. Infections should be brought under control, and suspected dietary deficiencies should be corrected. In some cases control of pain can be achieved by these measures alone; in others the occasional use of analgesics is required, and in a third group it is necessary to teach the patients how to avoid assuming a lordotic position. During rest, the legs should be bent at the hip and knee joints, and a thick hard pillow should be placed under the neck, in order to prevent the cervical and lumbar regions from assuming a lordotic position at night. Lordosis increases an existing constriction of the neural foramens,³⁰ as well as an associated displacement of the articular processes. Gentle active and passive bending, recommended as a limbering-up exercise during the morning, often helps patients to overcome the pain and discomfort experienced especially at this time of the day.

The use of back braces is rarely beneficial, probably because most of these appliances hold the spine in a position of lordosis. In fact, several of the patients in this series experienced material relief as soon as these braces were removed. Various modes of traction, used in the past and recommended by various authors, including myself, have not proved to be satisfactory in recent years and have been discontinued by me and my associates.

In 582 cases roentgen-ray therapy was used for the control of backache and of radicular nerve pain. The value of this mode of treatment is not generally recognized, and many authors believe that its effects are highly questionable. It is true that almost nothing is known about the mechanisms that underlie the results of small doses of radiation. Moreover, the application demands experience and requires the kind of personal supervision that the overburdened radiologist can ill afford to give. The doses and intervals have to be adapted to the case, the phase of the disease and sundry other factors. Hence the treatment cannot be standardized. In institutions where the pressure of more important work makes this personal supervision unfeasible, the results have been generally disappointing. Radiologists who are in the fortunate position to devote some time to this method find the results are worth the effort.

Using a technic previously reported,¹⁴ it was found that in 74 per cent of the patients the therapeutic effects were due to the radiation itself, but not to the associated psychologic factors. Permanent relief from pain and discomfort was obtained in 21 per cent of the cases, temporary relief in 55 per cent, and doubtful or negative results in the remaining 24 per cent. In patients in whom only temporary relief was achieved, repetition of roentgen-ray therapy proved to be effective in controlling recurrences. Treatment was given with 140 to 160 kilovolts, and 5 to 20 milliamperes, with 0.5 mm. copper and 1.0 mm. aluminum filtration, through portals 15 cm. square, the single doses measured on the skin being between 35 and 75r according to the duration of symptoms, with total skin doses of between 200 and 700r per series.

Among the patients who did not respond to the various measures above summarized, the majority had well-marked arthritic changes in the apophyseal joints at or above the level of the involved disks; some others presented bony impingement of the corresponding articular processes. In the latter group, subsequent treatment with body casts, traction and eventual spinal fusion did not prove to be satisfactory.

The best results of roentgen-ray therapy were noted in patients with trophic disturbances of the skin, muscles and bones in the peripheral segments corresponding to the involved disk. With striking uniformity these severe lesions disappeared within a number of weeks after the institution of roentgen-ray irradiation, and the disabled limbs resumed

normal function soon afterward. There seems to be no other mode of treatment by which these lesions can be arrested.

CONCLUSIONS AND SUMMARY

Disk lesions are about twice as common as is duodenal ulcer. This high incidence may be explained by the evolutionary development of the human spine. The vertebral column of man does not differ essentially from that of many quadrupeds; it is closely similar to that of the cow.³² This means that a system of bones and joints that was originally adapted to bear almost no vertical stress sustains in man the whole impact of the upright posture and locomotion. In some persons the vertebral bone is less resistant to strain than are the disks, but in a majority of adults the disk cartilages are the weakest parts of the spine. Wear and tear cause numerous minimal injuries from which the disk rarely recovers completely, since its cartilage cannot be effectively regenerated. Cartilage undergoes degeneration, with increase of fibrous tissue. The result is loss of turgor and volume of the disk. The same changes may be caused by a single severe injury and by certain diseases of the adjacent vertebral bodies from which the disk receives its nutrition. Disk rupture is one of the injuries which may be followed by degeneration. No matter what is the cause of the injury and degeneration, flattening of disks leads to narrowing of the corresponding intervertebral spaces, associated with displacement of articular processes, narrowing of the neural foramen and abnormal contact between vertebral bodies.

The clinical manifestations depend on these secondary alterations rather than on the degree of disk thinning. Narrowing of the neural foramen may cause radicular neuritis if the corresponding nerve root is compressed, but compression does not occur in every case because of the variable relations between the caliber of the nerve and the degree of constriction. Pain in the back and limitation of vertebral movements are less frequent and seem to be caused predominantly by diskogenetic involvement of the apophyseal joints.

The conspicuous predominance of symptoms experienced in radicular distribution in the periphery over symptoms felt in the spine itself is perhaps due to the fact that the disk, being devoid of nerves,³³ does not hurt when diseased. The most sensitive parts in its neighborhood are the nerve roots and the apophyseal joints. Arthritis of these joints develops in about 20 per cent of the cases of disk lesions and produces pain in the back with limitation of vertebral motion. In the majority of cases, however, the apophyseal joints remain intact, and symptoms of nerve-root compression develop without pain and rigidity of the spinal region involved. This means that in most cases lesions of disks cause symptoms felt in the limbs without symptoms felt in the back or neck.

PARENTERALLY ADMINISTERED AMINO ACIDS AS A SOURCE OF PROTEIN IN MAN*

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RECENT experiments have shown that the ten amino acids believed to be essential for the growth of rats¹ and for the formation of plasma proteins in dogs² are capable on intravenous or subcutaneous administration of replacing all or nearly all the dietary protein required by man for nitrogen equilibrium or retention and that the parenteral administration of these amino acids, supplemented with glycine, is very well tolerated by man, as it is by the dog. Aside from their fundamental interest, these observations appear to point to a valuable means of restoring body protein or protecting against its depletion in the diseased or injured person. Protein depletion is a serious complication that because of its insidious development frequently goes unrecognized until it reaches an advanced state. Among the hazards to which it predisposes may be mentioned lowered resistance to infection,^{3, 4} lowered resistance to intoxication⁵⁻⁷ and impaired healing of wounds.⁸⁻¹⁰ In many forms of illness or injury the dietary intake of protein is reduced or at best normal, whereas the need for it is usually increased.^{11, 12} Reduced appetite or impaired capacity for ingesting, retaining or absorbing protein may be responsible for the inadequate intake of protein.

Search for solutions acceptable to the body and capable of providing the nitrogen requirements on parenteral administration has been pursued of late and reviewed recently, and a fairly comprehensive bibliography has been compiled.¹³ The readiness with which the dog utilizes solutions of pure amino acids such as those listed in Table 1 contrasts with its lower tolerance for all other protein digests,^{2, 14-16} and prompted the clinical observations now in progress. The entire investigation will be reported later, but the initial observations are of sufficient interest to be recorded now. There follows the report of the case that formed the basis of this experiment.

CASE REPORT

The patient was a 63-year-old farmer who had developed a gastrojejunocolic fistula. Twenty-three years previously a gastroenterostomy had been performed for relief of pyloric obstruction and a perforating pyloric ulcer. He remained free from gastrointestinal complaints until a year previously, when he began to have diarrhea and lost weight. The fistula was discovered by x-ray and a colostomy was done proximal to it. Most of the lost weight was regained, but after ten months the fistula was still open. Operation was performed

for excision of the fistula and closure of an apparently non-functioning gastroenterostomy. The colostomy remained patent. Subsequently the patient did poorly. Abdominal discomfort, nausea and vomiting were associated with an inadequate intake of food and a marked decline in weight. After 4 weeks had elapsed, the colostomy was closed successfully, and because of the poor nutritional state and the possibility that parenteral feeding would be beneficial, the patient was transferred to the Metabolic Unit.

A careful and complete record of the respective weight or volume of the food or fluid received was kept throughout the investigation. All urine, feces, vomitus and gastric washings were saved and analyzed for total nitrogen by the macro-Kjeldahl procedure. The urine was also analyzed for its content of urea and ammonia nitrogen, by the method of Van Slyke and Kugel.¹⁷ The nitrogen content of the food was calculated from data published in standard tables of reference (Rose) and in a few instances from data furnished by the commercial processor of the food. The weight was obtained at frequent intervals and under as nearly uniform conditions as possible.

The composition of the amino acid mixtures is given in Table 1. Each mixture was stirred into distilled water just

TABLE 1. Composition of Amino Acid Mixtures.

AMINO ACID	MIXTURE Vh gm.	MIXTURE Vn gm.	MIXTURE Vx gm.
dl-threonine	7	7	7.4
dl-valine	8	8	11.1
dl-leucine	15	15	22.3
dl-isoleucine	7	7	10.4
l(+)-lysine hydrochloride	15	15	11.1
l(-)-tryptophane	2	2	3.7
dl-phenylalanine	5	10	11.1
dl-methionine	6	6	5.9
l(+)-histidine hydrochloride	3	3	3.7
l(+)-arginine hydrochloride	5	5	5.9
Glycine	27	25	7.4
Totals	100	103	100.0

below the boiling point. Filtration through hard paper was followed by autoclaving for 15 minutes at 15 pounds' pressure. The final volume of the solutions varied from 1250 to 1550 cc. and the reaction was approximately pH 5. The solutions were water clear and had a faint yellowish tinge after autoclaving.

Administration of the amino acid solutions was simple and rapid. The day's quota was divided into two equal injections, except for the first two days of Period 2 (Table 2), when the 50 per cent larger intake was given in three equal injections. Usually the morning dose was given subcutaneously, and the afternoon dose intravenously. Intravenous injections (50 gm.) were given on the average within 60 minutes and as rapidly as within 40 minutes (3.8 mg. of nitrogen per minute per kilogram of body weight). Subcutaneous injections were given on the average within 130 minutes and as rapidly as within 70 minutes (2.2 mg. of nitrogen per minute per kilogram of body weight).

Tolerance for the amino acid solutions was high. Its limits were not reached during this experiment, although the rates of injection used were more rapid than any recorded for protein-digest solutions with freedom from clinical disturbance. No rise in body temperature as a result of the injection was observed. In fact, during periods 5 to 10 (Table 2), the temperature did not rise above 98.6°F. On two occasions thrombosis of a forearm vein followed injections, more apparently as a result of inept venipuncture than of irritation from the solution. The lower pH of the solutions as compared with that of blood appeared to afford no intolerance. The plasma chlorides and the carbon dioxide combining power of the blood remained normal throughout the period of ob-

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||The amino acids used in this study were kindly supplied by Merck and Company, Incorporated, New York City.

servation with suitable administration of sodium and chloride. Similar high tolerance for these solutions has been found in dogs.¹⁶ In these animals the upper limits of tolerance without clinical disturbance are not reached by injections as rapid as 10 mg. of nitrogen per minute per kilogram of body weight, at which rate an adequate daily protein requirement is given within 15 minutes.¹⁶

The first 20 days (Periods 1 to 4) were characterized by severe pyloric obstruction, and the amount of food that

adequate amount of nitrogen and number of calories listed in Table 2. At least 107 gm. of nitrogen was lost during this period.

The patient was returned to the Surgical Service at the end of Period 4 because further radiologic studies suggested increasing pyloric obstruction and the possibility of a penetrating peptic ulcer. Nine days following the close of the period, a subtotal gastrectomy was performed with excision of a penetrating pyloric ulcer. After several transfusions and a

TABLE 2 Summary of Data

PERIOD	DAY	INTAKE		NITROGEN BALANCE				BALANCE*	CALORIC INTAKE†	WEIGHT
		Amino Acids	Food	Total Nitrogen	Urea and Ammonia Nitrogen	Undetermined Nitrogen	%			
		gm.	gm.	gm.	gm.	gm.		gm.	cal./day	kg.
1	1	14.7		13.6	78	3.9			510	44.12
	2	14.7		17.5	78	3.9				
	3	14.7		19.8	78	4.4			440	44.12
	4	14.7		17.7	75	4.5			270	
	5	14.7	0.5	17.7	79	3.8		-15.8	970	
2	6	22.1		20.6	70	6.1			800	44.30
	7	22.1		21.6	72	6.1			800	
	8	14.7		14.9	73	4.1			1140	
	9	14.7		16.2	73	4.4			1180	
	10	14.7	5.4	14.6	72	4.1		+3.74	1660	45.96
3	11	14.7		15.7	75	3.9			1390	
	12	14.8		15.5	65	5.4			1240	
	13	14.8		15.4	73	4.4			1390	
	14	14.8		14.6	73	4.0			880	
	15	14.8	7.2	15.7	74	4.1		+1.6	660	44.16
4	16	—	6.6	10.5	86	1.5			970	
	17	—	5.3	5.1	82	0.9			780	
	18	—	4.2	6.4	84	1.0			570	
	19	—	7.4	5.0	82	0.9			950	
	20	—	3.7	6.3	86	0.9		-10.7	470	43.50
Interval of 18 days, with subtotal gastrectomy on the 9th day										
5	21	—	10.3	5.0	72	1.4			1820	44.17
	22	—	11.4	5.9	78	1.3			1970	
	23	—	11.4	6.6	83	1.1		+11.1	1970	42.00
6	24	14.6	2.4	10.8	70	3.2			1560	
	25	14.4	2.4	14.6	73	4.0			1630	
	26	14.5	2.6	14.5	72	4.0			1920	41.29
	27	14.7	2.7	13.7	69	4.2			1890	
	28	14.7	3.6	14.4	73	3.9		+11.2	2510	41.59
7	29	13.1	3.6	12.6	70	3.8			3010	
	30	12.6	3.6	11.3	66	3.8			2770	42.30
	31	13.1	3.4	9.7	65	3.4			3000	42.53
	32	12.7	3.4	9.8	66	3.3			3000	43.06
	33	12.9	3.4	10.5	66	3.6		+20.6	3000	43.34
8	34	13.1	3.1	11.9	66	4.0			2740	43.02
	35	13.1	3.4	12.1	68	3.9			3000	43.50
	36	13.1	3.4	11.6	66	3.9			3000	
	37	13.1	3.4	11.9	66	4.0			3000	43.80
	38	13.1	3.4	11.9	65	4.2		+15.1	2720	43.89
9	39	—	16.0	8.3	77	1.9			3150	44.70
	40	—	16.0	7.6	83	1.3			3150	45.61
	41	—	16.0	10.2	85	1.5			3150	45.52
	42	—	16.0	9.6	84	1.5			3150	45.61
	43	—	16.0	8.6	84	1.4		+28.2	3150	45.89
10	44	—	16.0	8.9	83	1.5			3150	46.67
	45	—	16.0	8.1	82	1.5			3150	46.53
	46	—	16.0	7.9	84	1.3			3150	46.77
	47	—	16.0	8.7	85	1.3			3150	47.14
	48	—	16.0	9.3	85	1.4		+78.6	3150	46.95

*Nitrogen of feces and vomitus although not tabulated included

†Exclusive of amino acids

‡Nitrogen received from two transfusions not included

passed into the duodenum was small. Although the nitrogen intake of the first 5 days (Period 1) was adequate, on account of the amino acid injections (Mixture Vh), the calories from other sources were minimal and the loss of nitrogen amounted to about 3 gm. daily. During Periods 2 and 3 the patient continued to receive injections of amino acids (Mixture Vh and Mixtures Vh and Vn, respectively) and the caloric intake was increased by the daily intravenous infusion of 2000 cc. of 10 per cent glucose. This, together with small oral feedings of carbohydrate and fat, brought the daily caloric intake from all sources to an average of about 1500 calories. Nitrogen equilibrium was achieved in both periods. In Period 4, parenteral feedings were discontinued, with the result that the patient was able to eat and retain only the in-

adequate dietary regime the metabolic study was resumed on the 10th postoperative day (Period 5). A good positive diet containing about

Mixture Vn was resumed in Period 6, together with oral feedings of a diet consisting chiefly of carbohydrate and fat. More than 80 per cent of the nitrogen intake was from amino acids, and there was a satisfactory retention of nitrogen. The loss of weight noted in Periods 5 and 6, when nitrogen was being retained, appears to have been associated with discontinuance of the vigorous postoperative infusion of saline solutions, and suggests that this form of therapy may have been the cause of subclinical edema.

In Periods 7 and 8, Mixture Vx was given, and the caloric intake was increased. More nitrogen was retained, and there was a gain of 2.3 kilograms in weight. During the succeeding 10 days (Periods 9 and 10), the intake of nitrogen was entirely from food. Both the positive nitrogen balance and the gain in weight were somewhat greater.

A follow-up report from the patient 3 weeks later indicated continued improvement in general health and a continued rapid gain in weight.

COMMENT

When sufficient calories are provided, the nitrogen obtained from the amino acid mixtures is well utilized. It should not be concluded that the nitrogen obtained from natural foods is better utilized, for the following reasons. First, the amino acid mixtures used may not be the optimal ones. Second, more than 20 per cent of the nitrogen contained in them is present in those certain unnatural isomers that are said not to be utilizable by rats for purposes of growth.¹ Third, the patient was obviously in better condition at the end of Period 8, than at the end of Period 6, when the second course of amino acid solutions was begun, and it may be argued that his metabolic machinery was functioning more efficiently at the end of Period 8, thus giving a certain advantage to Periods 9 and 10, during which the natural food protein was tested.

There was no significant change in the concentration of plasma protein during the metabolic study. It averaged 5 gm. per 100 cc. during Periods 1 to 3 and rose to 5.6 gm. during Periods 6 to 8.

Of the urinary nitrogen, the amount not excreted as urea and ammonia was higher during the periods of amino acid injection than it was during the period of comparable nitrogen intake from food protein. This increase has been recorded in dogs receiving amino acids or protein digest parenterally.^{2, 14, 15} Its nature will be the subject of further investigation. It is apparently a function of the route of administration and not of the type of the nitrogen being administered, for it is not present in dogs when the same protein digest or amino acid mixture is given by mouth.

The glycine was originally added with the hope that it might furnish amino nitrogen for the *in vivo* synthesis of other nonessential amino acids. There is evidence from experiments in dogs that this hope is largely unrealized, but that the presence of glycine somewhat improved tolerance to the parenteral administration of the amino acid solutions.¹⁶

This report demonstrates the value in medical treatment of a synthetic mixture of pure amino acids given parenterally, but does not prove that this mix-

ture contains all the amino acids required by man. At all times, as indicated in Table 2, nitrogen of unknown amino acid composition was being consumed. It is equally true that the oral diets used by other workers testing the amino acid requirements of human beings contain 5 to 10 per cent nitrogen of unknown composition.^{18, 19} In another patient, to be reported soon, amino acid solution similar to Mixture Vx provided a positive nitrogen balance for a five-day period when it was the only source of exogenous nitrogen.

SUMMARY

A case is reported in which solutions of the amino acids essential for the growth of rats were given intravenously and subcutaneously without any clinical disturbance, and with satisfaction of the requirements of nitrogen equilibrium and formation of body protein. This fact is physiologically interesting and possibly of some practical importance in the treatment of patients.

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MEDICAL PROGRESS

SYPHILIS

G. MARSHALL CRAWFORD, M.D.*

BOSTON

PUBLIC-HEALTH ASPECTS

SOME extremely encouraging developments regarding the public-health aspect of syphilis, and particularly the sociologic facet, have been reported in publications during the last year. The Massachusetts law governing premarital examinations has not been in operation for sufficient time to allow a statistical survey of its usefulness. Talbot¹ has recently reported on the Connecticut law, with highly satisfactory findings. During the first seven years of its operation, 750 men and 690 women were found to have positive serologic tests for syphilis; this is equivalent to 14.1 per 1000 marriages. About 50 per cent of the patients diagnosed as having syphilis were unaware of their infection. Since the Connecticut law went into effect in 1936, the incidence of congenital syphilis has progressively decreased. The marriage rate dropped the first year, but since then it has increased steadily; in 1942 it was more than twice the 1932 figure. It may be said that the Connecticut law has been effective as a case-finding procedure and a measure for reducing the incidence of congenital syphilis. Physicians should have a greater incentive for taking routine serologic tests for syphilis. The education of the general public in regard to this disease should also be well served.

A consultation program on a statewide basis has been operating satisfactorily in New York. Kroll² reports on the operation of the plan, and it sounds quite workable. The state was divided into districts with a full-time consultant in each area. Local physicians were approached in two ways. Letters were sent out to all those in active practice; one of every eight made a response and the consultant visited their offices. The second approach was a visit to all physicians who had reported cases of syphilis under treatment, whether or not advice had been requested; one of every three of this group accepted assistance. Consultation may be obtained by mail or through a visit to the local physician's office with discussion of the case. An examination of the patient was carried out wherever possible, and such diagnostic procedures as dark-field examination, lumbar puncture and so forth were performed when requested. The problems of the participating physicians concerned late latent syphilis, the choice of drugs or the management of neurosyphilis in 50 per cent of the cases. The next 40 per cent of questions concerned the following in the order given: early syphilis, congenital infections, serologic interpre-

tations, infectiousness, syphilis in pregnancy and cardiovascular syphilis. This program has apparently stimulated greater interest among general practitioners and served to educate them in more capable practice. The result has been greater co-operation with the public-health authorities. In addition to the consultation program, diagnostic clinics are operated in large centers.

From the purely sociologic standpoint and aside from other laudable aspects, California has taken two worth-while steps. A venereal-psychiatric clinic has been opened in San Francisco.³ The purpose of this service is to provide re-education and readjustment for girls and women who have histories of promiscuous sex relations and who may spread or who are spreading venereal disease among the civilian population and armed forces. The socioeconomic background of these patients is studied, and every attempt is made to remedy their maladjustment. Emphasis is placed on rehabilitation and relocation of the patients through the co-operation of local agencies. A special court, the Separate Women's Court, has also been opened in San Francisco to meet the problem of sexually promiscuous women who are arrested.⁴ Every effort is made to provide means for adequate referral for first offenders who present a potentiality for re-education and readjustment. The medical co-ordinator of the Separate Women's Court is the chief of the Division of Venereal Diseases. These measures seem most rational.

A new approach to the source-finding and suppression of venereal disease has been suggested by Williams.⁵ His so-called "facilitation process" has been pursued in Vancouver, British Columbia, with considerable success. This approach to the control of venereal disease lies in the premise that the acquisition of a venereal disease is dependent on two factors: namely, the source of the infected person and the circumstances whereby the source is made accessible to the healthy person. Action dealing with the source has been a common procedure in all control campaigns. Action directed toward the "facilitators" to remove conditions rendering the source accessible is the key to Williams's plan. The facilitation process comprises those community conditions associated with the direct or indirect, witting or unwitting participants, usually for monetary gain of the third person, whereby persons suffering from common venereal disease are made accessible for intimate exposure to healthy persons. The facilitators or third-person participants, are madams, pimps and procurers with whom may be associated unethical

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physicians, lawyers, finance companies and real-estate agencies. Managers and owners of premises may also be in the ranks of the facilitators. The attitude of certain civic administrators, health departments and law-enforcement agencies may place the officials of these administrations, and also the public, in the position of being facilitators. Those engaged in the commerce of liquor are last, but by no means least. Dance halls, taverns, rooming houses and employees of these establishments, as well as taxicab-drivers, hotel clerks, bellhops and so forth, may be of great importance. Serious attention to such components of the facilitation process, as well as closing disorderly houses, has led to remarkable results in British Columbia. The Canadian Navy's monthly incidence of venereal disease on the West Coast has been only about half that on the East Coast. Canadian Army and Air Force statistics show a better record in the British Columbia district than in any other military area. These satisfactory figures substantiate Williams's claim for success in his campaign. He believes that "energy expended in the suppression of facilitation in a community is far more profitable from the public-health standpoint than the usual misdirected efforts at 'suppression of prostitution' which harassed the exploited, sick prostitute and left untouched the wealthy, healthy facilitator." This seems to be one of the most worthwhile campaigns for the control of venereal disease on record.

The widespread effect of the campaign of the United States Public Health Service to control venereal disease is reflected in innumerable articles. Practically every medical journal carries one or more publications in this vein from time to time, and there is considerable overlapping in their content. Attention can profitably be called, however, to police activities as outlined by Ness.⁶ A National Advisory Police Committee appointed by Federal Security Administrator Paul V. McNutt unanimously endorsed an eight-point agreement as a national standard for law-enforcement officers throughout the United States. This agreement was drawn up jointly by the War Department, the Navy Department and the Federal Security Agency as the official federal policy for the control of venereal disease. Point 6 of the agreement recognizes prostitution as the chief source of venereal disease. In those communities that have clamped down on prostitution, there has been no crime wave or increase in rape cases. On the contrary, this action has frequently resulted in corresponding improvements in the criminal situation. The National Advisory Police Committee has recognized that the repression of prostitution is not the only method of control to protect the health and welfare of the armed forces, war workers and girls engaged in prostitution. An intelligent over-all war-protection program is necessary. Such a program must provide measures for the social and economic rehabilitation of the girls

arrested, as well as the fundamental measures for attacking conditions which breed prostitution.

SYPHILIS IN THE ARMED FORCES

Encouraging figures on the incidence of venereal disease have been published by Weber.⁷ During World War I the rate was 86.7 per 1000. During 1941 the rate for the Army was 42 per 1000, and in the first six months of 1942 it had dropped to 38 per 1000. This is most heartening in view of the expected increase that has always accompanied the forays of Mars. Vonderlehr and Usilton⁸ have published an analysis of serologic reports of nearly 2,000,000 men of draft age up to the end of August 1941. This is the young adult male group, in whom the incidence of syphilis would be expected to be higher than that in any other. The rate of prevalence of syphilis, based on positive and doubtful blood tests among the selectees examined, was found to be 45.3 per 1000. The figures for white selectees in this group was only 17.4 per 1000. Most encouraging is the reduction in the incidence of venereal disease in the Navy.⁹ The rate for all venereal disease was 80 per 1000 in 1940, 51 per 1000 in 1941 and about 36 per 1000 in 1942. The trend is thus downward by 50 per cent over the three-year period, and the Navy venereal-control officers can be justly proud of this result.

The British have apparently been having more trouble than have we, according to published figures. The increase in venereal disease since the beginning of the present war has been serious enough to command special attention. The British public has been more reticent about publicity in regard to venereal disease than has the American public, and only recently have newspaper and magazine articles on this subject been printed. The Ministry of Health has issued a new defense regulation (No. 33B), under which it will be possible in certain cases to compel persons infected with venereal disease to undergo medical treatment.¹⁰ Taking the number of civilian infections in syphilis alone, the most trustworthy test of the wartime increase, there were 5000 in 1939, 5600 in 1940 and 7300 in 1941. If to this are added the infections among British military services, the total increase in syphilitic infections amounts to 100 per cent. Venereal disease in Scotland showed an even greater increase, the incidence there having more than doubled since the outbreak of the war. In Australia there had likewise been an increase in the incidence of early syphilis¹¹; until fairly recently all soldiers in the Home forces having syphilis were discharged from the army as medically unfit and instructed to report to their own physicians or local boards of health for treatment. Re-enlistment was possible after a satisfactory course of treatment. Australian Army personnel having syphilis are now discharged.¹² By a recent arrangement, infected soldiers are treated at special hospitals until no longer infectious, and are then transferred to a compa-

for duty while their weekly injections are continued. In addition, an educational campaign is under way in the Australian Army.

SYPHILIS IN INDUSTRY

The man hours lost by workers in war industry as a result of venereal infections have reached serious enough proportions to warrant more active attempts to control syphilis in their field. Schwartz and Markel¹⁴ have approached the problem from the standpoint of protecting the employee as well as the employer. The syphilitic worker, even in the primary or secondary stage of the disease, is a negligible source of infection to employees of the same sex. Neurosyphilitic patients should not be employed where lapses of consciousness, such as the dropping of explosives, may result in accidents. Workers having syphilis in the tertiary stage should not be employed where they are exposed to the action of nitrates and other nitrogenous compounds that have a marked effect on the vascular system or to lead and carbon disulfide, which affect the central nervous system. Even workers who have had adequate treatment for tertiary syphilis should not be exposed to the action of such compounds. Many occupational diseases can simulate syphilis in its various stages, and these are well portrayed in Schwartz and Markel's paper. This is a profitable publication for thorough study by all physicians engaging in industrial practice.

The Surgeon General of the United States Public Health Service has appointed an advisory committee to assemble current authoritative information and to formulate basic principles applicable to a program of venereal-disease control in industry. This committee has outlined the objective of such a program in regard to medical and public-health aspects and employees' problems, as well as those of the employer. Anderson et al.¹⁵ elaborate on these objectives and outline the manner in which the plan can be operated. It is emphasized as of the utmost importance that the results of medical examination be considered confidential as between the worker and the medical staff. Venereal-disease forms should be filed in the medical department for the use of the medical staff only, and not in an open file. Employees found to have syphilis should be referred to a reputable source for medical attention and not discharged so long as the industrial physician is notified at regular intervals regarding continuation of treatment. The plant physician making a tentative diagnosis of syphilis or gonorrhea should without delay acquaint the appropriate health authority with the facts of the case. It is properly emphasized that there is no reason for denying employment to an applicant or for discharging an employee because a medical report has given evidence of syphilis or gonorrhea, provided the worker co-operates satisfactorily in the treatment program. Nelson¹⁶ has written on the same problem in cogent fashion. One

point well emphasized is that there is no relation whatever between the blood test and the infectiousness of syphilis. Nelson further states that it is to the best interests of both industry and society to put the infected person to work or to keep him at his job contingent on such treatment as may be necessary. This is safer than to dismiss him with completely unsupervised treatment or none at all. Nelson states that the use of the blood test as a key to employment in general, for the purpose of excluding those who may be dangerous in certain occupations, is as ridiculous from the point of view of public safety, and as unsound medically, as it is unjust. In many industries the problem is already being intelligently handled. How soon it is to be solved in others will largely depend on whether the well-informed physician or the uninformed layman is to determine the medical policy.

An example of a well operated plan was published by Yeager.¹⁷ Since 1934 the Remington Arms Company has been giving complete physical examinations to all employees, including a blood serologic test for syphilis. Applicants in a communicable or a contagious stage of syphilis cannot be employed, in conformance with the Connecticut state law. New employees in the noninfectious stage can be hired provided they take adequate treatment, a plant physician keeping check on this. Provision can be made for treatment at clinics for applicants who are unable to pay, and the employee's disease is kept strictly confidential. Applicants or employees in a communicable stage are considered for employment after they have been rendered noninfectious by treatment. Although the Selective Service statistics show that Connecticut has the lowest percentage of syphilis in any state, the incidence among the employees of the Remington Company's Bridgeport works is even lower. The employees are most grateful to the company for making it possible to diagnose the condition, particularly those who had no previous knowledge of their infection or thought they were cured.

The control of venereal disease in industry will save time and money for all concerned, as pointed out by Anderson.¹⁸ It will also achieve a higher standard of efficiency and increase the industrial worker's earning capacity and life expectancy. The syphilitic blind cost society about \$10,000,000 a year, and paretic patients in state institutions cost another \$6,500,000. Congress appropriated \$12,500,000 for the control of venereal disease in 1943, and the states will raise some \$7,000,000. To each of these sums industry will contribute liberally through taxes. From the cost angle alone, therefore, industry has a considerable stake in venereal-disease control. The state health departments may have to provide mobile facilities for the employees in the smaller plants that have no regular medical service. One such department has a blood-test trailer operating among small plants and communities.

It should be pointed out that the safest worker regarding the spread of syphilis is one with a positive serologic test for syphilis who is under treatment, after passing the infectious stage; he or she is also immune to reinfection. If venereal-disease control can be furthered by education of industrial workers, and industry itself can be shown the fallacy of discharging workers on the basis of a positive serologic test alone, a great step will have been taken. Strikes in war plants arouse the indignation of the public because of wasted time and money and loss of production. Venereal disease can be responsible for these same losses.

EXPERIMENTAL RESEARCH

The vast amount of plasma in use by the armed forces and the rapid rise in the popularity of blood banks increase the importance of a study concerning the survival of *Treponema pallidum* in the various preparations. Ravitch and Chambers¹⁹ investigated this problem in regard to frozen plasma, with experiments on animals. They were able to show that human and rabbit plasma heavily inoculated with *Tr. pallidum* and frozen at -20°C . for forty-eight hours or longer is not infectious for normal rabbits.

A study of the similarities of several representative types of bismuth preparations used in the therapy of experimental syphilis has been reported by Clausen, Longley, Green and Tatum.²⁰ Five bismuth compounds in common use were employed, with both intramuscular and intravenous administration to animals. Their toxicity was studied and the therapeutic efficiency of each was computed. The similarity of the minimal curative dose, regardless of the route of administration, and the similarity in the toxicity of the various preparations when given intravenously suggested that basically all bismuth preparations ultimately act in a common form rather than in the form in which they are injected. The effect of ammonium chloride on the mobilization and excretion of bismuth in normal and syphilitic rabbits was studied by Brown, Kolmer and Rule.²¹ In the presence of massive doses of bismuth subsalicylate this effect of ammonium chloride may increase the toxic effects of the bismuth. In the treatment of acute testicular syphilis of rabbits, the increased mobilization of bismuth was without therapeutic value. In human beings, however, the opinion was expressed that this increased mobilization of bismuth may lead to an enhanced therapeutic effectiveness. It was pointed out that since acidosis increased the toxic effects of bismuth, it is not advisable to administer ammonium chloride to syphilitic persons predisposed to the acidotic state.

It would be ideal to have an arsenical preparation that could be used effectively by oral administration in the treatment of syphilis. Rosenthal²² has studied Mapharsen in this respect. Mice infected with a trypanosome were cured by oral doses. Rabbit

syphilis was then attacked in the same fashion, with satisfactory results. Glutathione and cysteine were found to decrease the toxicity of Mapharsen without effecting its therapeutic activity, and the drug was better tolerated when one of these was given. Similar work was carried out by Brown, Kolmer and Rule.²³ Working with rats, these investigators found that the trivalent arsenical drugs were far less toxic when given by oral administration than when injected intravenously. Mapharsen was least toxic by a large margin. Rabbits with acute testicular syphilis were then treated by the oral administration of trivalent arsenicals. In terms of arsenic administered, it was found that the therapeutic effectiveness of Mapharsen by oral administration is higher than in the case of arsphenamine and neoarsphenamine. The same group²⁴ then studied the toxicity and therapeutic effectiveness of arsenical preparations by intramuscular administration. Here again, Mapharsen was found to be of lower toxicity than the other drugs and of high therapeutic effectiveness. These results suggested that the intramuscular injection of Mapharsen in sterile peanut oil may prove to be of value in the treatment of human syphilis. A schedule of five daily intramuscular injections was projected for a massive arsenotherapy schedule for early syphilis. If clinical experiment should bear out this possibility, many of the dangers of massive therapy might be reduced.

There has been considerable disagreement regarding primary optic atrophy in neurosyphilis. It seems possible that visual damage in treated cases may be due to the syphilis itself, to the therapeutic agent or to a combination of factors. Longley, Clausen and Tatum²⁵ studied the experimental production of primary optic atrophy in monkeys, which were chosen since their eyes have been found to resemble those of human beings more closely than do the rabbit's. Five arsenical compounds were administered intravenously to different groups of animals in gradually increasing doses at weekly intervals. In these experiments, blindness was produced in monkeys in varying degrees by each of the drugs. The authors believe that this work provides an experimental basis for detecting the blinding potentialities of arsenical compounds for man. It also provides the means for a study of prophylactic procedure designed to reduce or eliminate optic atrophy as a sequence of chemotherapy for neurosyphilis. Tryparsamide amblyopia was studied by McDermott, Webster, Baker, Lockhart and Tompsett²⁶ from the standpoint of nutritional degeneration of the optic nerve in rats. Deficiencies of various vitamins were produced in certain groups of animals, and these with normal rats, were treated with tryparsamide. Only in the presence of adequate amounts of vitamin B complex (yeast) and vitamin A (cod-liver oil) did rats fail to develop degeneration of the optic nerve. This was found to be true whether or not they were treated with tryparsamide, although the latter in

tensified the degeneration. The implications of this work seem obvious.

PATHOLOGY

Autopsy material of the last twenty-five years at Yale University School of Medicine has been analyzed for syphilis by Rosahn and Black-Schaffer.¹⁷ Five thousand three hundred autopsies were performed during this time. Those done on persons twenty years of age or over numbered 3907, and of these 380 (9.7 per cent) had clinical, laboratory or post-mortem evidence of syphilis. In this group of 380 syphilitic patients there were 156 (41 per cent) with morphologic lesions of syphilis. Ninety (58 per cent) of these patients with anatomic lesions died primarily as a result of their syphilis. When the material was analyzed from the standpoint of sex incidence, it was found that women appeared to have a significant resistance to the tissue changes of late syphilis, and that this was independent of race. When the syphilitic and nonsyphilitic portions of this autopsy material were compared, it was found that the mere presence of syphilis significantly reduces longevity, regardless of whether or not tissue lesions result. Twenty per cent of nonsyphilitic patients survived after the age of seventy, as against only 10 per cent of those with syphilis. Life-insurance actuaries would do well to review these findings.

SYPHILIS AND CANCER

The prevalence of syphilis among a sample series of 7761 cancer cases was studied by Levin, Kress and Goldstein.²⁸ Of the 3151 male patients, 3.2 per cent were found to have been reported as syphilitic, and among 4610 female patients, 1.7 per cent had syphilis. Males with cancer of the tongue showed a greater prevalence of syphilis than did those with cancer of other sites, in the ratio of 5:1. Among females with cancer of the uterine cervix, the corresponding ratio was 3.5:1. This higher prevalence of syphilis is similar in both instances to that reported in other studies and has long been recognized.

MORPHOLOGIC DIAGNOSIS

An interesting variation in dark-field microscopy technic is suggested by Witlin.²⁹ This author recommends examining the slide under the low and high-dry objectives before applying oil to the coverslip. Time is thereby saved in locating the organism, and it can then be properly identified by observation under the oil-immersion lens. The importance of dark-field examination of lesions of the cervix is emphasized by Sharp, Alexander and Schoch.³⁰ It is stressed that although a cervical lesion may appear to be traumatic or merely an exacerbation of chronic cervicitis, a dark-field examination may reveal spirochetes. This applies particularly to the examination of contacts of known syphilitic patients and of patients with seronegative primary syphilis. The use of the dark-field in the diagnosis

of secondary syphilis has been portrayed by Agee.³¹ The employment of this technic in primary lesions of syphilis, genital or otherwise, and in moist papules is generally recognized as an essential diagnostic procedure. It is the advisability of searching for spirochetes in other types of skin lesions that Agee emphasizes. This is obviously intelligent when one considers that the presence of positive serologic tests with skin lesions suspected of being those of syphilis does not necessarily prove the case as secondary. Also, the beginning of treatment can be expedited by obtaining a positive dark-field reaction without waiting for a positive serologic report. Dry or closed secondary lesions can be abraded vigorously by means of a scalpel or dry gauze. If serum does not exude freely, it may be necessary to squeeze the area to express such material.

From time to time various stains for *T. pallidum* have been described. These procedures are useful under some circumstances where a dark-field condenser is not readily available or where the patient cannot be transported. Smears can be obtained in outlying communities and properly examined elsewhere within a comparatively short time. Perrin³² describes such a method, which in his hands has proved simple, rapid and reliable.

REINFECTION

The problem of reinfection versus superinfection versus recurrence of the infectious phase has always been a source of considerable discussion. There has been an apparent increase in reinfections since the advent of so-called "massive therapy," as will be shown below. This has brought up the advisability of reviewing the criteria of reinfection, and several papers on this subject have appeared. Schoch and Alexander³³ have expressed a somewhat altered concept of reinfection in view of their experiences, and record 10 cases. Four patients sustained reinfection following orthodox antisyphilitic therapy. Six of 103 patients were reinfected following a ten-day course of intensive arsenotherapy (1200 mg. of Mapharsen) for early syphilis. The details of these cases are reviewed, and for the most part they fit well into the category of reinfections. The authors state that whether or not the six cases of reinfection following intensive therapy are acceptable as such, they serve to emphasize the importance of developing new and more rapid epidemiologic approaches to syphilis when short-term intensive schedules of treatment are used. Schoch and Alexander offer a hypothesis to explain the fact that more reinfections seem to be occurring. This explanation intimates that patients with early syphilis treated by intensive methods are prevented by treatment from developing any immunity against reinfection, that the chemotherapeutic prophylactic effect of intravenous arsenotherapy disappears within a brief time after treatment ceases, and that such patients are prone to expose themselves so soon to the infectious

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CASE 30041

PRESENTATION OF CASE

A forty-nine-year-old housewife entered the hospital because of jaundice of four days' duration.

The patient was in fair health until about five weeks before admission, when she began to feel tired and run down. She developed a gnawing pain in the right upper quadrant. There was some numbness of the fingertips, and stiffness of fingers in the mornings. About two weeks before admission she had a shaking chill, with fever of 102°F. associated with sore throat, headache, running nose and generalized aches and pains. Ten days prior to entry, she had a crampy pain in the right upper quadrant lasting for a few minutes. The malaise, anorexia and coryza persisted. She had a cough productive of yellowish-brown mucoid sputum. The temperature was about 101°F. Four days before admission she noted jaundice of the skin and scleras. At the same time the urine became dark yellow, and the stools a light tan. She developed a severe headache and had waves of nausea but no vomiting.

Twelve years before her present admission the patient was admitted to another hospital for functional bleeding. She received 1400 milligram-hours of radium. Ten years later she was readmitted to the same hospital for essentially the same complaint. A dilatation and curettage was of no value, and about six months later she was given 2000 milligram-hours of radium. This was followed some months later by radiation proctitis. She was then transferred to this hospital, where a hysterectomy was performed ten months before her present entry, the diagnosis being pyometrium. At that time she also had a bilateral femoral-vein ligation following thrombophlebitis of the right calf. The proctitis improved with the removal of fecal impactions, and she was discharged well, seven months before the present admission.

Physical examination showed an obese woman in no distress. There was moderate icterus of the skin and scleras. Small petechiae were peppered over the lower abdomen, left arm and lower back. The axillary and inguinal lymph nodes were small

*On leave of absence.

and nontender. The heart was percussed 1 cm. to the left of the midclavicular line. The sounds were regular and of good quality. There was a soft systolic murmur, heard loudest at the apex. The lungs were clear. The abdominal wall was pendulous. The liver edge was palpable three or four fingerbreadths below the costal margin. It was firm, smooth and slightly tender. The spleen was palpable three fingerbreadths below the costal margin; it was not tender. Pelvic examination showed a bilaterally lacerated cervix covered with an atrophic mucosa. There was slight tenderness in the right vault, but no masses could be palpated.

The blood pressure was 140 systolic, 75 diastolic. The temperature was 98.6°F., the pulse 72, and the respirations 24.

Examination of the blood showed a red-cell count of 4,300,000, with 12.5 gm. of hemoglobin. The white-cell count was 4000, with 72 per cent neutrophils, 22 per cent lymphocytes and 6 per cent monocytes. The platelets were slightly diminished, the red cells showed slight variation in size and shape, with many target cells, and the neutrophils showed a shift to the left. A blood Hinton test was negative. The urine was dark amber and acid, with a specific gravity of 1.020; there was no albumin, but a ++ bile test. It was positive for urobilinogen in 1:20 dilution (normal, 1:10). The stools were light tan and guaiac negative. The bleeding time was 6 minutes, and the clotting time 15 minutes. A fragility test showed beginning hemolysis in 0.40 per cent and complete hemolysis in 0.28 per cent sodium chloride solution. A tourniquet test gave 25 petechiae per square centimeter after fifteen minutes with a pressure of 100 mm. of mercury (normal, 6 to 20). The blood sugar was 104 mg. per 100 cc. The direct van den Bergh was 6.6 mg., the indirect 9.6 mg. The total protein was 5.2 gm. per 100 cc., with 3.2 gm. of albumin and 2.0 gm. of globulin. The nonprotein nitrogen was 31 mg. per 100 cc. The prothrombin time was 27 seconds (normal, 18 seconds). The hematocrit was 46.5. A cephalin flocculation test was ++++ in twenty-four hours and ++++ in forty-eight hours. There was 100 per cent retention of bromsulphalein.

Plain films of the abdomen showed several ring shadows in the right upper quadrant that had the appearance of gallstones. A gastrointestinal series and films of the chest were negative.

The patient was given a high-carbohydrate, high-vitamin B, low-calorie and low-fat diet, supplemented daily by 500 cc. of intravenous dextrose. In the next few days the jaundice definitely increased. She had several, occasionally severe but usually moderate colicky attacks of right-sided abdominal pain. The pain was mostly in the upper quadrant and on one or two occasions radiated to the shoulder.

On the tenth hospital day she became orthopneic, with a feeling of substernal oppression, and

forced to sit up. There was profuse sweating. This episode presumably lasted for a few minutes. The temperature was 100°F., the pulse 96, and the respirations 24. The white-cell count was 5200, with 82 per cent neutrophils. The urine had a + test for albumin and a ++ test for bile. The stools became brown and remained so. The direct van den Bergh was 12.7 mg., the indirect 17 mg. The prothrombin time was 49 seconds (normal, 20 seconds). The hematocrit was 40.0, and the non-protein nitrogen 17 mg. per 100 cc.

The patient's condition became progressively worse. She was nauseated, retched considerably and vomited occasionally. She was given daily intravenous dextrose and repeated transfusions. On the sixteenth hospital day the van den Bergh was 8.2 mg. direct, and 13.8 mg. indirect. The stools became guaiac positive. The urine gave a +++ test for albumin and a ++ test for bile, and was positive for tyrosine crystals (Morner's test).

She died on the eighteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. MARIAN ROPES: May we see the x-ray films?

DR. GEORGE W. HOLMES: The gallstones are obvious. The position of the gallstones gives some idea concerning the position of the lower border of the liver. You can vaguely make out the liver shadow. It is not enlarged so far as I can see, nor abnormal in shape. In this film the diaphragm seems to be quite high on the right side so that even though the lower border is not unusually low, the liver might still be somewhat enlarged. It is also possible that the film was taken at the end of expiration rather than of inspiration. I see nothing abnormal in the lung fields. The heart shadow is well within normal limits, both in size and shape.

As I understand the story the patient received radium treatment and was said to have had proctitis following it. Apparently an effort was made to study the rectum and lower sigmoid by means of a barium enema, a rather careful search having been made for any abnormality in that region, but I should say that this is a rather normal looking colon throughout. We have some films of the stomach, including the duodenal loop, that appear to be normal. In the cases with serious complication following heavy radiation to the pelvis, the organ most likely to be injured is the small bowel. Patients will stand a good deal of injury to the large bowel and recover, but the same amount of injury to the small bowel often causes considerable difficulty. There is no indication here of such injury — no collection of gas and no dilated loops of small bowel suggesting obstruction, such as might occur after heavy radiation.

DR. ROPES: This case presents a picture with various confusing features. It is apparent that the patient had severe liver-cell damage, and it is also probable that she had some obstruction to the biliary

flow. I judge that her death was due fundamentally to the liver damage. The underlying etiology and sequence of events leading to this final picture, however, are not equally clear. Various etiologic possibilities should be considered. A malignant neoplasm, either primary or secondary in the liver, or primary in any part of the biliary system, seems unlikely in view of the rapid course of the disease, the variation in jaundice, and the marked evidence of liver-cell damage. Pylephlebitis, idiopathic hepatitis, cholangitis, cholelithiasis and cholecystitis should be considered. Before discussing these possibilities however, it might be well to summarize the evidence indicative of the extent to which the jaundice was due to liver-cell damage and the extent to which obstruction may have played a role.

The clinical evidence gave little information in this respect except the fact that bile in some quantity reached the gastrointestinal tract at all times during the disease, with resulting tan or brown stools and with normal bilirubin in the urine. In the laboratory evidence one finds definite indication of liver damage as indicated by the tyrosine crystals in the urine; the high cephalin flocculation test is presumably further indication of severe liver-cell damage, as is perhaps the leukopenia. The low globulin is a surprising finding and helps me not at all in differentiation in this respect. The exceptionally high bromsulfalein retention would not have been found unless there had been severe liver-cell damage, even if obstruction were present. The van den Bergh gives a suggestion of obstruction to biliary flow. A high direct van den Bergh, particularly as high as it was in this case, is unlikely in pure parenchymatous liver disease. I am told that a direct-indirect ratio of 60 to 80 — this patient had 70 — is suggestive of obstruction, whereas in pure parenchymatous liver disease the ratio rarely goes over 50. How well corroborated that is, I do not know.

With this evidence I should like to return to the etiologic possibilities. Pylephlebitis must be considered. It is intriguing to consider whether one could thereby relate the pelvic inflammation — the pyometrium — to the present illness. It would be unusual to have an asymptomatic period of six months, and an absence of fever and leukocytosis. The marked evidence of liver damage is difficult to explain on the basis of pylephlebitis. Idiopathic hepatitis and cholangitis would explain most of the picture. The early onset of pain in the right upper quadrant and the recurrent attacks of moderately severe colicky pain are unusual in this condition but not entirely inconsistent with it. The gallstones cannot be overlooked. So far as we know, they were rather large and presumably in the gall bladder. Gallstones, particularly if in the common duct, with some obstruction and with some cholangitis, could form the basis for this terminal picture. The presence of the splenomegaly raises the question of an

underlying cirrhosis. I believe, however, that the enlargement of the spleen could be ascribed to the severe liver damage. The tender large liver — at least clinically large — and the large spleen are consistent with pylephlebitis, with idiopathic hepatitis or with hepatitis associated with cholelithiasis.

In conclusion I think that this patient had severe parenchymatous liver disease and that she also had cholelithiasis. Whether the former could in any way be related to the latter etiologically, I do not know. It seems somewhat improbable. I also doubt that she had pylephlebitis as an underlying cause of the severe liver disease.

DR. J. H. MEANS: I saw this patient every day while she was in the hospital and followed her carefully. Our line of reasoning followed Dr. Ropes almost exactly and led to the same diagnosis. We believed that she died of severe parenchymatous liver disease, a hepatitis of some sort. We did not know of what variety. We also tried to connect it with the pelvic sepsis and wondered if she had pylephlebitis, but in my note I stated that I thought that that was unlikely because she had had a considerable interval of good health in between. The question of cirrhosis was considered. The size of the spleen was interesting. I thought the liver was enlarged when she first came in, and I am interested to know what the pathologist has to say about that. The clinician and radiologist often have different views about the size of the liver, but the pathologist is able to settle the matter because he can weigh it. I thought that the liver was firm and smooth but could not feel a definite edge.

The impressive thing on the ward was the steady downhill course, the patient becoming sicker and sicker every day in spite of all we could do. Dr. Chester M. Jones saw her several times, and Dr. Arthur W. Allen was asked to see her because the question arose whether she should be explored, but that was decided against. Dr. Jones laid a great deal of weight on the color of the stools. Indeed, he said to me one day, "If the stools remain brown, do not let the surgeons do a laparotomy." They remained brown, and the surgeons did not want to do a laparotomy. We thought that the gallstones had little or nothing to do with the picture in all probability. She had not taken any medicine that we could recognize as a liver toxin, so we called it hepatitis of unknown origin. We did think at the end that she might have had acute yellow atrophy, although we could not prove it. We also thought of the possibility of an acute yellow atrophy that supervened on a cirrhotic liver but could not establish that diagnosis.

DR. JACOB LERMAN: Did the liver change in size?

DR. MEANS: I cannot answer that. I do not know that we proved that it did.

DR. PAUL ZAMECNIK: Was catarrhal jaundice considered?

DR. MEANS: Yes, at entry. She did not appear to be particularly sick and we thought that that was a reasonable diagnosis to consider. The blood picture was consistent with it. In fact she was almost too well to have catarrhal jaundice. She rapidly became sicker and sicker and we abandoned that diagnosis as inadequate.

DR. ZAMECNIK: It is occasionally followed by hepatitis.

DR. MEANS: That is true. Catarrhal jaundice is hepatitis, is it not? It is really just a matter of degree. We wondered when she died if we had treated her adequately. We had given her a diet low in fat and high in everything else, pushed with vigor. Dr. Jones thought that we had done everything possible.

CLINICAL DIAGNOSES

Intrahepatic disease.
Acute yellow atrophy?
Cholelithiasis.

DR. ROPES'S DIAGNOSES

Parenchymatous liver disease.
Cholelithiasis.

ANATOMICAL DIAGNOSES

Subacute yellow atrophy of liver.
Splenomegaly.
Ascites.
Cholelithiasis.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy showed a liver of normal size, weighing 1400 gm. It was greenish brown and extremely friable; as one touched it, it broke. It had on the surface a few elevations, as if some attempt at regeneration had occurred. From the gross appearance we thought that it was an acute yellow atrophy of the liver.

Microscopic examination showed that practically all the liver cells had been destroyed. There were a few small islands of regeneration, so that this was perhaps a subacute yellow atrophy. The point that Dr. Means brought out — namely, that catarrhal jaundice is merely a mild form of acute yellow atrophy — is probably correct. We believe that it is exactly the same disease. Aspiration biopsies of the livers of patients ill with catarrhal jaundice have shown diffuse hepatitis, with inflammatory cells in the early stages, followed by areas of necrosis and finally by connective-tissue proliferation.¹ If the disease is not severe, the patient gets well; if severe, death is due to acute yellow atrophy or subacute yellow atrophy, depending on how long the course runs.

The spleen was enlarged, weighing 550 gm., the usual finding in atrophy of the liver. There were

forced to sit up. There was profuse sweating. This episode presumably lasted for a few minutes. The temperature was 100°F., the pulse 96, and the respirations 24. The white-cell count was 5200, with 82 per cent neutrophils. The urine had a + test for albumin and a ++ test for bile. The stools became brown and remained so. The direct van den Bergh was 12.7 mg., the indirect 17 mg. The prothrombin time was 49 seconds (normal, 20 seconds). The hematocrit was 40.0, and the non-protein nitrogen 17 mg. per 100 cc.

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Examination of the blood showed a hemoglobin of 95 per cent, a red-cell count of 4,400,000 and a white-cell count of 7900, with 60 per cent neutrophils. The urine was normal. A blood Hinton test was negative.

Stereoscopic x-ray films of the left shoulder showed the clavicle to be normal. There was a well-defined soft-tissue mass in the supraclavicular area on the left that extended downward behind the clavicle and apparently into the space between the scapula and the chest wall (Fig. 1). This mass showed several flecks of calcification. The lowermost areas of calcification lay close to the undersurface of the scapula. A questionable separate mass was seen in the axilla. The undersurface of the scapula seemed thinned by the mass. X-ray films of the chest, abdomen and long bones showed no evidence of pathology.

An operation was performed on the thirteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. CARROLL B. LARSON: The initial complaint was pain in the left arm at the shoulder, especially on vigorous movement or by pressure on the shoulder. In the subsequent history I am not sure when they say "pain over the shoulder" whether they mean over the scapular joint. It might make a difference.

DR. ROBERT R. LINTON: I believe it was directly over the shoulder.

DR. LARSON: Do you recall whether it was worse at night than during the day, which is characteristic of deep bone pain?

DR. LINTON: I do not believe that it was.

DR. LARSON: Apparently there was no mechanical obstruction to the usual motions of the arm. The fact that he could not throw a ball, however, suggests that there was some difficulty.

This story does not suggest a lesion in the region of the epiphysis or a lesion disturbing the blood supply because of no inequality in arm lengths at the end of a three-year period. The difference in the circumferences of the two arms could have come from lack of use of the left arm rather than from the lack of development.

At rest the arm "was carried with the elbow and wrist in partial flexion." I am not sure what to make of that. It may be possible that, with a mechanical difficulty in the shoulder, such a position was a comfortable one for carrying the arm. The inability to rotate the left shoulder might have been because of pain or mechanical obstruction.

The tremor could be accounted for by lack of muscular development. Anyone with weak muscles cannot sustain a position for any length of time without tremor.

Perhaps we might see the x-ray films at this point. There is a fullness in the supraclavicular region that does look like a "holding forward" of the shoulder,

which gives it a shortening in the anteroposterior view. The joint may or may not be deformed.

DR. MILFORD SCHULZ: The chest is normal except for the deformity of the left shoulder girdle. Here we see the soft-tissue mass extending above the clavicle. These probably are the areas of calcification referred to. In addition one cannot see any bone structure in the body of the scapula. Of course the scapula is normally quite thin in this area, and that may be the reason. From the x-ray films there is no way of knowing whether the calcification is in the soft tissue or represents new-bone formation.

DR. LARSON: The child was perfectly well following the toxin-antitoxin injections. On that basis we



FIGURE 1. Roentgenogram of Left Shoulder Showing Soft-Tissue Mass in Supraclavicular and Subscapular Regions.

can exclude tuberculosis and chronic infection, which might have originated in bone and ended up in a soft-tissue mass giving this picture. The chest was negative and there was no cough or pain referable to the chest, so that we can probably exclude anything coming from the chest.

That leaves us with a tumor in this region but we are not sure whether it arose from bone or from the tissues around the bone. The fact that it was producing symptoms for three years is against a malignant tumor, but does not exclude it. Let us consider the bone tumors that occur in a child of this age.

With Ewing's tumor one would expect more new-bone formation. Lymphoblastoma occurs in this group of children and this is one of the locations which it can occur; frequently the tumor extends

itself from the bone and produces a soft-tissue mass. In this boy there was little bone destruction compared to the size of the mass. With malignant lymphoma there is usually some clinical evidence of malignant disease, such as cachexia and marked anemia. I cannot, however, exclude lymphoblastoma as a possibility. Giant-cell tumor can be excluded almost immediately. There was not enough bone destruction, and the patient was in the wrong age group. A chondrosarcoma can occur in this area, and there may be areas of calcification within it. The mass may have developed from malignant degeneration in a chondroma. I cannot exclude that. Fibrosarcoma must also be considered. This mass overlay an area where the subscapularis muscle originates, and a soft-tissue tumor like a fibrosarcoma can develop in the subscapularis itself. In a primary nerve tumor one would expect more persistent pain and a greater number of neurologic findings.

Cartilaginous exostoses might fit in with a bone condition of this sort. It is most unusual for exostoses to reach this point of growth without producing more pronounced mechanical symptoms than this boy had, and there should be more evidence of new-bone formation. Hence, I exclude this diagnosis.

That leaves us with malignant tumor, even though the patient did not show constitutional signs of malignancy after three years. I believe that it was of the chondroblastic type, but it might have been fibroblastic or lymphoblastic.

DR. WILLIAM B. BREED: I do not understand whether you believe that the tumor originated in the bone.

DR. LARSON: As I stated before, the decision is difficult. The tumor could have originated in the bone and could have exteriorized itself, or it could have produced the entire x-ray picture by external pressure. I favor the former.

DR. LINTON: We were indefinite in our minds preoperatively concerning where the lesion originated. I rather thought that it was a malignant lesion, which would necessitate a shoulder-girdle amputation. Dr. J. C. White saw the boy because the question of nerve tumor was raised. It was decided that, if the tumor was not malignant, he would try to remove it by lifting the brachial plexus and the supraclavicular vessels. He started the operation by dividing the clavicle and exposing the tumor. It was obvious that the tumor was malignant and I completed the operation by doing a shoulder-girdle amputation and removing the entire clavicle. I did a block dissection and did not try to determine where the tumor had arisen. It was our feeling that it

probably arose from the brachial plexus. Extensive dissection of the cervical lymph nodes was also performed since some of the nodes in the posterior triangle were enlarged and appeared to be involved. The roots of the brachial plexus were divided close to the intervertebral foramina.

CLINICAL DIAGNOSIS

Tumor of clavicle (neurofibroma?).

DR. LARSON'S DIAGNOSIS

Chondrosarcoma of scapula, low grade (possibly fibrosarcoma of subscapular region or lymphoblastoma of scapula).

ANATOMICAL DIAGNOSIS

Neurogenic fibrosarcoma of subscapular region.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The tumor was large and fibrous and measured 14 by 9 by 6 cm. There was erosion of the scapula and of the clavicle, but it seemed to us to be the type of erosion that results from long-standing pressure against bone. There was no direct invasion of bone. The mass did, however, invade some of the surrounding muscles.

Microscopically it was a low-grade neurogenic fibrosarcoma, that probably arose from one of the branches of the brachial plexus. The regional lymph nodes were negative.

DR. LINTON: From the surgical point of view, if it was a low-grade malignant process, such as a fibrosarcoma, I believe that the best thing to have done is what we did.

DR. CASTLEMAN: The boy was seen seven months after operation and was perfectly well, going to school and playing just like any other boy. His only complaint was tenderness in the upper portion of the operative field when it is washed, apparently due to the severed nerve roots close to the skin. Fourteen months after operation, however, the patient re-entered the hospital because of a recurrent nodule in the neck. The mass was located in the upper lateral portion of the operative field; it involved the lower lateral end of the sternal mastoid muscle and was adherent to the first rib. The nodule, which measured 7 by 3 by 3 cm., and the first rib were removed; on microscopical examination it was found to comprise neoplastic tissue identical with that of the original tumor.

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SHARE THE BLOOD!

THERE is an urgent, almost dramatic, need for blood donors to furnish plasma for our fighting men, and the medical profession, which should be such a potent factor in promoting this vital enterprise, is, in too many instances, handicapping it. Healthy civilians, both men and women, who need encouragement to give blood at safe and reasonable intervals are being deterred from it, frequently for insufficient reasons. We are not yet awake to our opportunity and our obligation, for the supply is inadequate and the need will soon become desperate as the time for invasion draws near.

A remarkable organization for the collection of human blood plasma has been developed. This was

the result of a request made in May, 1941, by the surgeons general of the Army and Navy to the American Red Cross and the Division of Medical Sciences of the National Research Council. The function of the Red Cross has been to procure the donors, that of the National Research Council to supervise the professional services.¹ Through its various centers, the Red Cross met its quota of 4,000,000 pints of plasma in 1943; this year 5,300,000 pints will be required, and it must be noted that, owing to broken appointments, rejected volunteers and bloods, and certain irreducible technical losses, nearly 1250 persons must offer to give their blood for each 1000 units of dried plasma finally made available.

The blood collecting center in Boston, the only one in northern New England, is equipped to handle, during its six-day, sixty-eight-hour week, 800 donors daily, attaining, at times, a maximum speed of two bleedings per minute. The substation in Lynn and the three mobile units, operating at distances greater than twenty-five miles from Boston, are each equipped to bring in an additional 1000 pints weekly. The actual number of donors bled at the Boston center recently dropped to between 400 and 550 per day, and a large number of these are war workers and service men. The civilian population is not doing its share.

The safety and health of the donor are carefully protected. Each donor must be free from disqualifying disease and must have a normal temperature at the time of bleeding, as well as a hemoglobin level of 80 per cent or over by the Tallqvist method and a systolic blood pressure between 100 and 200. No donor is accepted oftener than five times in a year, with a minimum interval of eight weeks between donations. This interval seems conservative in view of the studies of Fowler and Barer,² who found that the average drop in hemoglobin of 2.3 gm. after the removal of 555 cc. of blood was restored on the average in approximately fifty days, the time being somewhat longer for women than for men, and that the rate of regeneration did not seem to be affected by repeated donations.

Psychic factors in certain persons may be more important deterrents to blood donating than physical ones. Let us all, however, when the oppor-

tunities come to give advice on the subject, weigh the evidence objectively, and encourage rather than discourage, unless we are certain that a person's health may suffer unduly from this act of mercy.

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TUBERCULOSIS AND THE WAR

THE effect of war on tuberculosis death rates is generally considered to be inevitable and adverse. Heretofore it has always seemed to be so, although the slight increases in mortality observed in this country in 1917 and 1918 were more than compensated for by the subsequent accentuation of the downward curve. Anticipating that tuberculosis may again be "one of the camp followers of war," a committee of the American Trudeau Society* surveyed the personnel of the sanatoriums in this country and reported a distinct reduction during 1942. It is certain that this decrease in numbers, continuing on through 1943, is placing an ever-increasing burden on those who are left to operate the sanatoriums.

The war is also having an effect on the symbiotic relations between man and the tubercle bacillus. The armed services are rejecting, and thereby uncovering, many of the dangerous carriers among young men — those whose disease is symptomless but who nevertheless have open lesions from which they may freshly expose and widely spread the infection. From the millions of men examined at the induction stations, it is estimated that 25,000 had been diagnosed at the end of last year to have a disease that neither they nor their friends would have suspected under prewar conditions. And how are these patients, many of whom need sanatorium treatment, going to be accommodated by the currently restricted personnel of the sanatoriums?

Tuberculosis workers, who for some years past have been extending their case-finding activities, are thus suddenly having found for them more cases than they can conveniently care for. Morbidity

**Personal Problems of Sanatoria Resulting from War Conditions*, Report of a study made by the Committee on Sanatorium Standards, American Trudeau Society. 39 pp. New York: National Tuberculosis Association, 1943.

rates should go up, but there will not be more actual sickness — it will merely be more completely recognized. The mortality rates need not go up at all, for most of the cases will do as well as they would have if they had not been recognized, and many of them do better. Furthermore, fewer contacts will result.

No evidence has yet been uncovered to indicate that the downward trend of the tuberculosis death rate has been seriously affected. Whether it will be adversely influenced by a prolonged continuation of the war is a purely relative matter, and is really an insignificant speculation in comparison to the total interests similarly involved. On the whole it seems that the war will accelerate the antituberculosis effort by forcing a decreased personnel to dedicate itself to an increased volume of labor: just as the training of doctors and engineers is being accelerated, just as the shipbuilders are launching an incredibly large number of ships, and just as the entire nation is bending itself to the task ahead. The *Journal* has sufficient confidence in all the forces involved to make a humble prediction that the war years will not show an increase in the mortality of tuberculosis in the United States. This statement is not a mere prophecy — it is an expression of confidence in the ability, ingenuity and steadfast qualities of those who specialize in the care and the cure of tuberculosis.

MEDICAL EPONYM

RUMPEL-LEEDE SIGN

Theodor Rumpel (1862-1923), director of the Barmbecker Krankenhaus in Hamburg and chief physician of the Second Medical Service of the Allgemeines Krankenhaus, presented "Photographien von Scharlachkranken mit multiplen Hautblutungen [Photographs of Scarlet-Fever Patients with Multiple Skin Hemorrhages]" at a meeting of the Aerztlicher Verein in Hamburg on June 1, 1909. A report appears in the *Deutsche medizinisch Wochenschrift* (35:2297, 1909). A portion of the translation follows:

These hemorrhages, which also occur spontaneously on the forearm and in the bend of the elbow, in the area where the exanthem is most marked, may be induced by mechanical stimuli, particularly by the application of Bier's compression cuff to the upper arm, and are then of value in the differential diagnosis of scarlet fever.

Carl S. Leede (b. 1882), then assistant to Professor Rumpel and later a practitioner of internal medicine in Seattle, Washington, described "Hautblutungen durch Stauung hervorgerufen als diagnostisches Hilfsmittel beim Scharlach [Skin Hemorrhages Elicited by Congestion as a Diagnostic Aid in Scarlet Fever]" in the *Münchener medizinische Wochenschrift* (58:293-295, 1911). A portion of the translation follows:

At the request of [my] chief, Dr. Rumpel, who directed attention to the differential diagnostic significance of the phenomenon at the meeting of the medical society June 13, 1909, every case of scarlet fever was systematically subject to congestion by means of a rubber cuff applied to the upper arm so that the veins stood out distinctly while the pulse remained palpable.

Hereupon, almost without exception, among cases of scarlet fever (several hundred were examined) more or less marked skin hemorrhages appeared. . . .

In my experience a *negative* result of the congestion test may be used as an almost certain criterion against scarlet fever, whereas a *positive* result may be evaluated only together with other symptoms.

We perform the congestion test at the present time as follows:

A broad rubber cuff is placed about the upper arm above the elbow so that the veins stand out distinctly; the hand becomes blue, but the pulse remains palpable. After ten to fifteen minutes we loosen the cuff and examine the tender skin of the fold of the elbow, at the same time making the skin anemic by means of stretching it, whereupon the petechiae stand out more distinctly as a dark spray.

We call the congestion test positive even though we find only a moderate number of petechiae.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

PERLEY — Roscoe D. Perley, M.D., of Melrose, died January 21. He was in his eighty-first year.

Dr. Perley received his degree from Harvard Medical School in 1896. He was a former member of the staffs of the Massachusetts General Hospital and the Boston Lying-in Hospital and was on the surgical staff of the Melrose Hospital for forty years. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, a son and a daughter survive.

RICH — Herbert L. Rich, M.D., of Attleboro, died January 23. He was in his seventy-ninth year.

Dr. Rich received his degree from Tufts College Medical School in 1898. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow and a brother survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CHANCROID, GRANULOMA INGUINALE AND LYMPHOGRANULOMA VENEREUM MADE REPORTABLE

As provided by the General Laws, Chapter 111, Section 6, the Department of Public Health has defined and made reportable the diseases *chancroid*, *granuloma inguinale* and *lymphogranuloma venereum*. Physicians in Massachusetts are required to report these diseases directly to the De-

partment of Public Health under the same conditions, rules and regulations as now pertain to the reporting of syphilis and gonorrhea; and further, to use the same report form that is now provided by the department to report syphilis and gonorrhea for the purpose of reporting these three other diseases. For the present, it is suggested that the physician write on the report form the name of the disease he is reporting and strike out the words, "syphilis" and "gonorrhea."

Prepared spreads of material collected from the undermined edges of the suspected chancroidal ulceration or, still better, from the aspirated pus of the bubo may be submitted by the physician to the Bacteriological Laboratory, State House, Boston, for diagnosis. A spread of macerated tissue from the active edge of a lesion thought to be granuloma inguinale may also be sent to the laboratory. Antigen for skin testing for lymphogranuloma venereum will soon be available from the Antitoxin and Vaccine Laboratory for free distribution to private physicians. Literature dealing in detail with the management of these diseases by the physician may be obtained from the Department of Public Health.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

CLINIC	DATE	CLINIC CONSULTANT
Haverhill	February 2	William T. Green
Lowell	February 4	Albert H. Brewster
Salem	February 7	Paul W. Hugenberger
Brockton	February 10	George W. VanGorder
Springfield	February 16	Garry deN. Hough, Jr.
Worcester	February 18	John W. O'Meara
Pittsfield	February 21	Frank A. Slowick
Fall River	February 28	Eugene A. McCarthy
Hyannis	February 29	Paul L. Norton

MISCELLANY

THE ELLA SACHS PLOTZ FOUNDATION

During the twentieth year of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation, eighteen applications for grants were received by the trustees, thirteen of which came from the United States, the other five coming from five different countries in Europe, Asia, North and South America. In the twenty years of its existence the Foundation has made four hundred and eighty-one grants which have been distributed to scientists throughout the world.

In their first statement regarding the purposes for which the fund would be used, the trustees expressed themselves as follows:

1. For the present, researches will be favored that are directed toward the solution of problems in medicine and surgery or in branches of science bearing on medicine and surgery.
2. As a rule, preference will be given to researches on a single problem or on closely allied problems, it is hoped that investigators in this and in other countries may be found, whose work on similar or related problems may be assisted so that more rapid progress may be made possible.
3. Grants may be used for the purchase of apparatus and supplies that include the payment of unusual technical assistance, including technical assistants, which are, and tend to be, essential for the support of exceptional circumstances.

In the past few years the policy outlined in paragraph 2 has been neglected. Grants will be given in the sciences closely related to medicine without reference to special fields. The maximum size of grants will usually be less than \$500.

Applications for grants to be held during the year 1944-1945 must be in the hands of the committee before April, 1944. There are no formal application blanks but letters asking for aid must state definitely the qualifications of the investigator, an accurate description of the research, the size of the grant requested and the specific use of the money to be expended. In their requests for aid applicants should state whether or not they have approached other foundations for financial assistance. It is highly desirable to include letters of recommendation from the directors of the departments in which the work is to be done. Only applications complying with the above conditions will be considered.

Applications should be sent to Dr. Joseph C. Aub, Massachusetts General Hospital, Fruit Street, Boston.

CORRESPONDENCE

APPEAL FOR BOOKS

To the Editor: This is a personal appeal. We need your help. The National Victory Book Campaign terminated on December 31, 1943. An unfortunate impression has become current, that the campaign was wound up because it had collected all the books needed. Nothing could be further from the facts. — The men in our armed forces and in the Merchant Marine need books *desperately*.

The Massachusetts Victory Book Committee has been formed to carry on in Massachusetts from where the National Victory Book Campaign left off. The Massachusetts Committee has set its minimum goal at 250,000 volumes. All types of books, in good condition, are welcome. Biographies, travel, science, religion, but especially good fiction — mysteries, westerns and comics — are in demand. Visualize how men on long sea voyages, on dreary coast patrols, in lonely outposts and in the remote parts of the world yearn for something to read.

The Massachusetts Victory Book Committee needs your help. It asks you personally and in your official capacity to enlist the wholehearted efforts of your readers.

Every book donated will reach the armed forces where it is most wanted. Distribution will be handled by Special Service officers of the Army and the Welfare officers of the Navy. The merchant-marine and the Red Cross military hospitals will also receive their share.

You are familiar with the slogan "Get the Vote Out." This committee's slogan is "Get the Books Out." It is a big job, but it must be done.

Books should be left at local public libraries or at the nearest Information Center of the Massachusetts Committee on Public Safety. This committee will do the rest.

JOHN HEARD, *Secretary*
Massachusetts Victory Book Committee

13 Commonwealth Avenue
Boston 16

NOTICES

UROLOGY AWARD

The American Urological Association offers an annual award "not to exceed \$500" for an essay (or essays) on the result of some specific clinical or laboratory research in urology. The amount of the prize is based on the merits of the work presented, and if the members of the Committee on Scientific Research deem none of the offerings worthy, no award will be made. Competitors shall be limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. All interested should write the secretary for full particulars.

The selected essay (or essays) will appear on the program of the forthcoming meeting of the American Urological Association, June 19-22, 1944, Hotel Jefferson, St. Louis, Missouri.

Essays must be in the hands of the secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee, on or before March 15, 1944.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, February 3, in the classroom of the Nurses' Residence, at 7:15 p.m. Dr. Francis L. Weille will speak on the subject "Treatment of Sinusitis." Dr. Elizabeth DeBlois will be chairman.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston

Lecture Hall, 9-10 a.m.

MEDICAL CONFERENCE PROGRAM

Wednesday, February 2 — To be announced. Dr. John D. Adams.

Friday, February 4 — Clinical Importance of Cold Hemagglutinins. Dr. Cutting B. Favour.

Wednesday, February 9 — The Diagnosis of Pancreatic Disease. Dr. Joseph H. Pratt.

Friday, February 11 — Clinicopathological conference. Dr. Chester S. Keefer and Dr. Harold E. McMahon.

Wednesday, February 16 — Constipation. Dr. Edwin T. Whitney.

Friday, February 18 — Some Postwar Aspects of Malaria. Dr. William C. McCarthy.

Wednesday, February 23 — Mechanisms Predisposing to Pneumonia. Dr. Dwight O'Hara.

Friday, February 25 — Visualization of the Biliary Tract. Dr. Charles G. Mixer.

On Tuesday and Thursday mornings Dr. S. J. Thannhauser will give medical clinics on hospital cases.

WASHINGTONIAN HOSPITAL

The second lecture in a series on various aspects of alcoholism, arranged by the Washingtonian Hospital and being given under its auspices and that of the Committee on Alcoholism of the Boston Council of Social Agencies, will be held at Zero Marlborough Street, Boston, at 7:30 on Friday evening, February 11. The speaker will be Dwight Anderson, LL.B., director, Public Relations, Medical Society of the State of New York, and his topic, "Alcohol and Public Opinion."

NEW ENGLAND DERMATOLOGICAL SOCIETY

The regular meeting of the New England Dermatological Society will be held in the Skin Out Patient Department of the Massachusetts General Hospital on Wednesday, February 9, at 2 p.m.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 3

THURSDAY, FEBRUARY 3

*9.00-10.00 a.m. Medical clinic. Dr. S. J. Thannhauser, Joseph H. Pratt Diagnostic Hospital.

7:15 p.m. Treatment of Sinusitis. Dr. Francis L. Weille. New England Hospital for Women and Children.

FRIDAY, FEBRUARY 4

*9.00-10.00 a.m. Clinical Importance of Cold Hemagglutinins. Dr. Cutting B. Favour. Joseph H. Pratt Diagnostic Hospital.

SATURDAY, FEBRUARY 5

*10.00-11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

(Continued on page xiii)

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PERITONEOSCOPY IN LIVER DISEASE*

EDWARD B. BENEDICT, M.D.†

BOSTON

IN a series of 435 peritoneoscopies¹⁻³ performed during the last few years at the Massachusetts General Hospital, the question of liver disease arose in 331, or 70 per cent, of the cases examined. The instrument designed by Ruddock^{4, 5} was used in all cases. It is therefore evident that one of the chief uses of the peritoneoscope is in the diagnosis of liver disease.

When one considers that many of these patients are seriously ill and that in most of them an exploratory laparotomy is out of the question, the value of a precise diagnosis by peritoneoscopy is apparent. In comparing peritoneoscopy with exploration it should be pointed out that the former procedure requires only a 1-cm. incision under local anesthesia, an overnight stay in the hospital and minimum risk or discomfort to the patient. In 435 peritoneoscopies there have been 3 deaths (0.7 per cent) probably attributable to the procedure: one, a death from heart failure in a patient with multiple lung abscesses, coronary disease and possible echinococcal cyst of the liver; the second, a death due in part to hemorrhage eight days after peritoneoscopy with liver biopsy for extensive metastatic carcinoma; and the third, a death three weeks after perforation of the large bowel in a severely ill patient proved by peritoneoscopy to have advanced tuberculous peritonitis. These patients were all extremely sick, and it was probably unwise to subject the first one to peritoneoscopy, but many very sick patients can safely undergo the procedure if carefully watched by a competent assistant.

The preparation of the patient with liver disease for peritoneoscopy is of considerable importance, for frequently there is jaundice and liver damage. If the prothrombin time is prolonged, vitamin K is administered to reduce the bleeding tendency. Morphine and its derivatives, as well as the barbiturates, are to be avoided. Chloral hydrate may be safely substituted. Otherwise the patient is prepared as for any laparotomy, including an abdominal shave and scrub, and emptying of the stomach and

bladder. The usual site of puncture for inspection of the liver is in the midline just above the umbilicus. The technic of the procedure has been described in previous reports.¹⁻⁵

In a general way the cases of liver disease may be divided into two groups—the malignant and the nonmalignant. The 260 cases of liver disease in this series were classified as shown in Table 1.

TABLE 1. Classification of Cases of Liver Disease.

MALIGNANT		NONMALIGNANT	
Metastatic carcinoma	170	Cirrhosis	73
Primary carcinoma	5	Cholangitis	2
Melanotic sarcoma	1	Banti's disease	2
Malignant lymphoma	1	Lymphangioma	2
Total	177	Polycystic liver	1
		Echinococcal cyst.	1
		Sarcoid	1
		Enlarged liver	1
		Total	83

In the remaining 71 cases there was found to be an essentially normal liver. From the above tabulation it is evident that carcinoma and cirrhosis are by far the commonest diagnoses. So the question often to be decided by peritoneoscopy is the following: Is there any disease in the liver and, if so, is it cancer, cirrhosis or something unsuspected?

The cases referred for peritoneoscopy because of liver disease usually fall into one of the following groups:

Metastatic carcinoma. In this group there is a positive or presumptive clinical diagnosis of carcinoma of the breast, bronchus, esophagus, stomach, pancreas, colon, rectum, prostate or the like, and before planning medical, x-ray or surgical treatment it may be of great importance to know whether or not there is metastatic disease in the liver.

Hepatomegaly. Is one dealing with metastatic or primary carcinoma, cirrhosis, hepatitis, sarcoma, echinococcal cyst, polycystic liver or some other liver disease?

Ascites. Is this due to cirrhosis, carcinoma or tuberculous peritonitis?

Jaundice. Is the diagnosis toxic cirrhosis, biliary cirrhosis, malignant neoplasm, hepatitis or some other infectious process?

*From the Massachusetts General Hospital.
†Instructor in surgery, Harvard Medical School; associate visiting surgeon, Massachusetts General Hospital.

Doubtful clinical findings. What is the precise diagnosis?

Primary carcinoma of liver.

Metastatic Carcinoma

In this group the primary source is oftener in the stomach than in any of the other organs. Peritoneoscopy was performed in 95 cases of carcinoma of the stomach, 75 of which showed no metastases and 20 of which did show metastases. Thus, a laparotomy was avoided in 20 cases (21 per cent). During a five-year period (1937-1941), 263 patients with cancer of the stomach were explored surgically without peritoneoscopy and in 39, or 15 per cent, the cases were found to be inoperable because of liver metastases. If peritoneoscopy had been performed in these cases, thirty-nine laparotomies might have been avoided and over a year in hospital days saved.

CASE 1. J. K., (M.G.H. U-334286), a 56-year-old Russian porter, was first admitted to the hospital complaining of abdominal pain of 5 weeks' duration, associated with anorexia, nausea, vomiting and a weight loss of 15 pounds during the previous 6 weeks.

Physical examination showed slight resistance and tenderness in the epigastrium. There was no palpable mass and the liver was not felt. A large carcinoma of the stomach was reported by x-ray.

Peritoneoscopy revealed several yellow, umbilicated lesions in the liver, characteristic of metastatic carcinoma. Numerous, small nodules were seen on the anterior surface of the stomach consistent with carcinomatous invasion of the serosal surface. A biopsy was obtained from one of the lesions in the liver. The pathological report was metastatic carcinoma. Laparotomy was therefore not done.

Clinically this case was operable. The patient was only fifty-six years old and was well developed and nourished, and no abdominal mass was palpable. Except for the positive evidence of metastatic cancer in the liver at peritoneoscopy, he would probably have been subjected to a fruitless exploratory laparotomy.

If, on the other hand, no metastatic disease is demonstrable by peritoneoscopy, the patient should be explored surgically. Sometimes, as in the following case, when a patient appears clinically to be inoperable a favorable peritoneoscopy report encourages a successful resection.

CASE 2. M. J. (M.G.H. U-99960), a 77-year-old, unemployed Irishman, was admitted to the hospital complaining of indigestion and an abdominal lump. He had been perfectly well until 3 months before admission, when he gradually developed epigastric distress and soreness after meals. Four weeks previously he had noted a lump in the epigastrium.

Physical examination disclosed a midepigastric, apple-sized movable mass. X-ray examination showed extensive cancer of the distal half of the stomach.

Peritoneoscopy revealed a normal liver and no evidence of peritoneal metastases or of extension of the growth through the gastric wall. Operation was therefore undertaken, and although there were carcinomatous lymph nodes along the lesser curvature, a gastric resection was successfully carried out.

In addition to cancer of the liver metastatic from the stomach, peritoneoscopy has in many cases demonstrated metastatic disease in the liver when

the primary source was in the breast, bronchus, esophagus, pancreas, colon, rectum or prostate or was of undetermined origin. In some of these cases, exploratory operation was thus avoided.

Hepatomegaly

CASE 3. G. S. R. (B.M. U-389474), a 35-year-old lumber salesman, entered the hospital because of enlargement of the abdomen of 1 week's duration. For 12 years there had been an excessive intake of alcohol, with anorexia for 6 months. There had been a recent 10-pound weight loss.

Physical examination showed jaundice, enlargement of the liver to below the umbilicus and ascites. The temperature varied from 98 to 102°F. A clinical diagnosis of alcoholic cirrhosis was made but, because of the large liver and the fever, malignancy was also considered.

Peritoneoscopy showed a granular, slightly nodular liver of mottled brown, red and yellow color. There was no evidence of malignancy. A biopsy resulted in a diagnosis of cirrhosis, alcoholic type.

In this case of hepatomegaly with jaundice, ascites and weight loss, peritoneoscopy confirmed the clinical diagnosis of alcoholic cirrhosis and excluded carcinoma.

CASE 4. F. H. S. (B.M. U-305683), a 71-year-old man, was referred to the hospital with a diagnosis of carcinoma of the stomach. He gave a history of anorexia and a 25-pound weight loss of 3 months' duration. There was also increasing fatigue and left-sided gas pain occurring 1 to 2 hours after meals.

Physical examination showed a small, elderly man with evidence of recent weight loss. The left lobe of the liver appeared to be enlarged. X-ray examination showed rigidity of the middle third of the lesser curvature of the stomach with narrowing of the antrum. The findings were those of carcinoma of the middle third of the stomach.

Peritoneoscopy was advised to determine whether or not metastases were present in the liver. Contrary to expectation, it showed a granular, almost hobnail liver, suggestive of cirrhosis. A small amount of ascitic fluid was also found and aspirated. A biopsy of the liver resulted in a diagnosis of toxic cirrhosis. Because of these findings no operation was performed. About 3 months later the patient died, and autopsy showed carcinoma of the stomach with metastases to the retroperitoneal and mesenteric lymph nodes and to the peritoneum, advanced portal cirrhosis of the liver, acute generalized fibrinous peritonitis, ascites and arteriosclerosis.

This case is presented to show how peritoneoscopy revealed an unsuspected cirrhosis of the liver in a patient known to have carcinoma of the stomach. Laparotomy was avoided.

CASE 5. I. M. P. (M.G.H. U-309910), a 60-year-old Negress, entered the hospital because of weakness and discomfort in the epigastrium for 4 months.

Physical examination was essentially negative except for a smooth, firm mass in the epigastrium and the right upper quadrant of the abdomen, which was thought to be liver. Differential diagnoses by various members of the staff included metastatic carcinoma, cirrhosis, syphilis, melanotic sarcoma, lymphoma, hemachromatosis, amyloid disease and echinococcal cyst. Various laboratory and x-ray studies failed to give a positive diagnosis.

Peritoneoscopy showed the liver edge to be sharp but somewhat thick. The surface was granular and reddish brown. There was no evidence of malignancy. A biopsy resulted in a diagnosis of nonspecific hepatitis. One month later, when the patient was seen in the Out Patient Department, she was feeling well, her appetite was good, and the liver was still enlarged.

In this case of hepatomegaly, peritoneoscopy explained the enlarged liver by a positive diagnosis of hepatitis.

Certain other cases of hepatomegaly are of interest and may be included in this group. Briefly summarized, they are as follows:

CASE 6. M. G. T. (M.G.H. U-286198), a 71-year-old woman, was admitted with masses in both upper quadrants thought to be an enlarged spleen and liver. The clinical diagnosis was possible acute disseminated lupus or possible Gaucher's splenomegaly.

Peritoneoscopy showed masses in both upper quadrants due to extensive metastatic carcinoma involving both lobes of the liver. The biopsy report was metastatic adenocarcinoma.

CASE 7. E. E. (M.G.H. U-202726), a 52-year-old woman, was admitted complaining of anorexia and abdominal discomfort. A deep-lying, hard, nodular mass in the right upper quadrant and the epigastrium was clinically diagnosed as retroperitoneal sarcoma or an enlarged liver.

Peritoneoscopy demonstrated extensive carcinomatous implants in the liver. The biopsy report was metastatic adenocarcinoma.

CASE 8. O. L. (M.G.H. U-179499), a 60-year-old man with a history of extreme alcoholism, was admitted complaining of epigastric pain and tenderness. A hard, tender mass was found in the right upper quadrant. The clinical diagnosis was possible cirrhosis, or possible lymphoma.

Peritoneoscopy revealed extensive carcinoma of the liver. The biopsy report was metastatic adenocarcinoma, with the primary source not determined.

CASE 9. J. F. M. (M.G.H. U-360839), a 57-year-old woman, entered the hospital with a history of easy fatigue, dyspnea, cough, nausea and vomiting. The liver was not palpable to several examiners, each of whom reported that he was unable to make a diagnosis. Another observer, however, thought the liver was enlarged, with some epigastric tenderness. X-ray examination confirmed a diagnosis of enlargement of the liver.

Peritoneoscopy revealed a liver filled with umbilicated, yellow nodules characteristic of carcinoma. The biopsy report was metastatic adenocarcinoma, Grade 3.

CASE 10. N. L., A 30-year-old, alcoholic man, entered the hospital because of an enormous liver that he himself had felt. The presumptive diagnosis was cirrhosis.

Peritoneoscopy, however, showed no evidence of cirrhosis, but demonstrated that the anterior surface of both lobes contained numerous slightly elevated, smooth, rounded, yellowish-gray lesions from 1 to 3 cm. in diameter, consistent with metastatic carcinoma, although not typically nodular or umbilicated. The biopsy report was lymphosarcoma.

In the last case, the clinical diagnosis of alcoholic cirrhosis was changed by peritoneoscopy, and the presumptive peritoneoscopic diagnosis of carcinoma was changed by biopsy to lymphosarcoma.

Ascites

CASE 11. L. L. (M.G.H. U-340612), a 55-year-old, Italian-born laborer, entered the hospital because of progressive enlargement of the abdomen of 2 months' duration, associated with anorexia and a dull pain in the left upper quadrant. All his life he had drunk two glasses of wine a day.

Physical examination revealed a greatly distended abdomen with slightly dilated superficial veins. A fluid wave was present. The liver was palpable about 8 cm. below the costal margin. The tip of the spleen was felt to descend to the iliac crest. There was also a hard, palpable, semicircular mass in the rectum 2 cm. above the prostate. The clinical diagnosis was cirrhosis of the liver, but carcinoma of the rectum with secondary implants in the liver was also considered.

At peritoneoscopy 7000 cc. of cloudy, yellow fluid was aspirated. The peritoneal surfaces throughout the abdomen

were covered with gelatinous, tapioca-like, nodular, translucent material, characteristic of metastatic carcinoma. The liver edge appeared sharp and the surface did not appear cirrhotic. The latter was, however, partially covered with numerous translucent, metastatic lesions that did not appear to involve the parenchyma. The liver edge was at the costal margin. The palpable masses were neither the liver nor the spleen but were large, carcinomatous masses, probably involving the omentum. A biopsy at the peritoneum resulted in a diagnosis of metastatic colloid carcinoma.

In this patient with marked ascites and upper abdominal masses thought to be liver or spleen, the clinical diagnosis was alcoholic cirrhosis, but peritoneoscopy revealed a generalized carcinomatosis.

CASE 12. B. V. D. (B.M. U-395034), a 29-year-old unmarried woman, entered the hospital because of swelling of the abdomen of 2 months' duration. For 9 months her appetite had been poor. For about a year she had noted that she was easily fatigued and had not felt well enough to work. For many years she had taken large amounts of alcohol, including a quart of sherry daily, as well as some brandy.

On physical examination the liver was found to be markedly enlarged, extending 5 fingerbreadths below the costal margin. The spleen was also palpable about three fingerbreadths below the costal border. There was moderate ascites but no jaundice. The presumptive diagnosis was alcoholic cirrhosis.

Peritoneoscopy confirmed this diagnosis and showed the liver to be pale, mottled and yellow. A biopsy of the liver resulted in a diagnosis of acute alcoholic cirrhosis.

The patient was kept in the hospital for over a month, receiving a high-protein and high-vitamin diet, several blood transfusions. The liver, spleen, and the spleen hardly palpable. Peritoneoscopy was repeated at the end of 1 month's treatment, at which time the liver appeared essentially normal in size, with a brownish-red surface. A second biopsy showed less fat and definitely more fibrous tissue. Alcoholic hyalin was still present, but the process was much less acute.

In this case of moderate ascites with a presumptive diagnosis of alcoholic cirrhosis, peritoneoscopy gave positive confirmation of this diagnosis and when repeated at the end of a month demonstrated definite improvement as a result of treatment.

Other cases in this group in which ascites was a marked feature and in which the differential diagnosis of liver disease always presented itself may be briefly mentioned as follows:

CASE 13. O. N. (B.M. U-338963), a 41-year-old man, had ascites and hepatomegaly. Following resection of carcinoma of the sigmoid, x-ray examination demonstrated an enlarged liver and spleen with esophageal varices, making a clinical diagnosis of cirrhosis likely, although metastatic carcinoma was also a strong possibility.

Peritoneoscopy showed extensive carcinomatous implants in the liver and some possible implants on the peritoneum. A biopsy of the liver resulted in a diagnosis of metastatic adenocarcinoma.

This case was most unusual. In spite of the demonstration of esophageal varices, metastatic cancer of the liver rather than cirrhosis, was present.

CASE 14. H. G. (M.G.H. U-389058), a 62-year-old woman, had a history of diarrhea, loss of weight, anorexia and vomiting for 2 months. Physical examination showed the abdomen to be distended with fluid and a large, nodular mass in the epigastrium. Proctoscopy showed a nodular lesion, entirely submucosal. At peritoneoscopy 1500 cc. of yellow, blood-tinged fluid was aspirated. Because of a large omental mass, only a part of the liver could be seen, the anterior surface of

which appeared entirely normal. A large, pearly-gray mass with numerous excrescences on it was seen in the lower abdomen and pelvis. Several biopsies were obtained that resulted in a diagnosis of metastatic carcinoma of the peritoneum.

The patient went rapidly downhill and died, and autopsy confirmed the finding of widespread abdominal carcinomatosis arising in the stomach and involving the wall of the rectum and both ovaries. The liver was normal except for infarction.

CASE 15. G. L. (B.M. U-385439), a 59-year-old woman, had an abdomen distended with gas and fluid. A mass in the right side of the abdomen was thought from x-ray examination to be liver but clinically was apparently not related to the liver.

At peritoneoscopy 9000 cc. of yellow, bloody fluid, which was under pressure, was aspirated. The liver did not appear to be abnormal. The peritoneal surfaces throughout were studded with numerous implants that appeared typical of carcinoma. Several biopsies were obtained that showed the diagnosis to be metastatic spindle-cell sarcoma, possibly of ovarian origin.

CASE 16. M. S. O'B. (B.M. U-189703), a 70-year-old man, gave a history of enlargement of the abdomen for 1½ years, with several taps yielding grossly bloody fluid. There was no marked weight loss. In spite of a negative history of alcoholism, the presumptive clinical diagnosis was cirrhosis of the liver.

At peritoneoscopy 750 cc. of thin, bloody fluid was aspirated. The liver appeared normal. Occupying the entire left side of the abdomen was a reddish-purple mass, partly covered with omentum and appearing extremely vascular and cystic. Diagnosis at the conclusion of peritoneoscopy was a possible large splenic or omental cyst.

Laparotomy revealed a large hemangiosarcoma, probably of retroperitoneal origin, which was successfully removed. X-ray treatment was then given. A year and a half later the patient was doing well; peritoneoscopy was repeated and there was no evidence of recurrence.

Although liver disease was not seriously considered in the following case, ascites was the presenting symptom and cirrhosis had to be excluded.

CASE 17. D. L. (B.M. U-299241), a 49-year-old woman, had distention of the abdomen of 4 weeks' duration with anorexia, easy fatigability and loss of weight.

At peritoneoscopy 5000 cc. of straw-colored fluid was aspirated. The liver appeared normal. Multiple cystic implants from 1 to 2 mm. in diameter were seen on the peritoneum throughout the abdomen and pelvis. The examiner's diagnosis was abdominal carcinomatosis, probably of ovarian origin, but the biopsy report was tuberculosis.

Jaundice

In this group jaundice was the outstanding sign. Ascites and hepatomegaly were frequently present. The differential diagnosis included carcinoma of the liver, toxic cirrhosis, biliary cirrhosis, bile stasis, hepatitis or some other infectious process.

CASE 18. M. S. (B.M. U-351346), a 77-year-old woman, entered the hospital because of jaundice of 1 month's duration and weakness of 6 months' duration. There had been some pain in the right back, dating from a fall 8 months before admission. There was no history of alcoholism. The liver was not definitely palpable, but there was dullness four fingerbreadths below the right costal margin. The spleen was not palpable. There was no ascites. No esophageal varices were demonstrable by x-ray. Because of these findings, cirrhosis of the liver of ordinary type was thought to be unlikely, and the presumptive diagnosis was carcinoma of the pancreas or biliary tract. A positive clinical diagnosis was impossible. A Graham test was negative. A brom-sulfalein test showed 70 per cent dye retention.

Peritoneoscopy demonstrated a hobnail liver and a spleen enlarged to about twice the normal size. A biopsy of the liver resulted in a diagnosis of cirrhosis, unclassified.

In this jaundiced patient without a history of alcoholism, the most likely clinical diagnosis was thought to be malignancy, but peritoneoscopy revealed cirrhosis.

CASE 19. L. D. O'B. (B.M. U-396744), a 57-year-old woman, entered the hospital with a chief complaint of jaundice of 8 months' duration. Fourteen months prior to admission she had had a cholecystectomy at a local hospital. Six months later painless, progressive jaundice developed. She was operated on again at the same hospital and told that she had adhesions. The jaundice did not improve, and 3 months later she was again explored at the same hospital, with the same result. Although her appetite had been good, she had lost 60 pounds in 14 months.

Physical examination showed an intensively jaundiced patient with a hard, irregular mass involving the entire upper abdomen and extending into the right lower quadrant. Biliary cirrhosis following trauma to the common duct and carcinoma obstructing the biliary system was considered the most likely clinical diagnoses.

Peritoneoscopy showed the left lobe of the liver to be at the level of the umbilicus and the right lobe extended below the iliac crest. The surface throughout was smooth and grayish-black, with fine white mottlings and striations. No nodules were seen and there was nothing to suggest neoplasm in the liver. The spleen was not visible. A biopsy of the liver resulted in a diagnosis of biliary cirrhosis.

Exploratory laparotomy was later performed. The hepatic duct was found to end blindly and a vitallium tube was inserted to connect it with the duodenum.

In this severely jaundiced patient, peritoneoscopy excluded metastatic malignancy in the liver and established the diagnosis of biliary cirrhosis.

Doubtful Clinical Findings

CASE 20. A. M. (M.G.H. U-283167), a 35-year-old clerical worker, entered the hospital because of loss of appetite and easy fatigue. About 3 years before admission he had begun to have vague abdominal discomfort and epigastric fullness. Six months prior to admission he had been troubled with a slight cough productive of only a small amount of mucoid sputum.

Physical examination disclosed a large, firm mass in the left upper quadrant that was thought to be spleen. The liver was not felt. X-ray study of the chest demonstrated mottled, increased density in both upper lung fields, with a cavity in the right infraclavicular area. There was also some fine mottling in the left lower lung field. The films were interpreted as bilateral tuberculosis. One of the consultants believed that the x-ray picture, as well as the enlarged spleen might be explained on the basis of sarcoid.

Peritoneoscopy disclosed a spleen extending just below the level of the umbilicus, that was brown and smooth throughout except for three or four, grayish nodules of pinpoint size just above the splenic notch. The liver did not appear to be enlarged, but the anterior surface throughout both lobes was mottled with irregular, fine, gray striations. The capsule was extremely firm. A satisfactory biopsy, however, was obtained and the microscopic report was sarcoid.

In this case the presumptive clinical diagnosis was pulmonary tuberculosis and splenomegaly of undetermined cause. Peritoneoscopy showed that the whole process was due to sarcoid.

Primary Carcinoma of Liver

The following 5 cases of primary liver-cell carcinoma seem worth while reporting in some detail, as follows:

CASE 21. P. B. (M.G.H. U-150174), a 50-year-old man, entered the hospital complaining of upper-abdominal pain, epigastric distress, a weight loss of 25 pounds in 2 months and an upper-abdominal mass. The use of alcohol was denied.

Physical examination showed an irregular, hard, tender mass in the epigastrium, descending with respiration, which was probably liver. The spleen was not palpable. There was no jaundice or ascites. Esophageal varices were not demonstrable by x-ray. Since the mass in the epigastrium was so definitely tender and the patient was running a temperature up to 101°F., a diagnosis of liver abscess or malignancy was considered and peritoneoscopy was undertaken.

At that time the liver presented a slightly mottled, cobblestone appearance in one area, but there was nothing to suggest liver abscess or carcinoma. The biopsy was possible hemangioma.

Since the patient continued to run a temperature, exploratory laparotomy was performed, which revealed an abscess well within the substance of the liver and therefore not visible by peritoneoscopy. The abscess cavity was drained and another biopsy of the liver resulted in a diagnosis of carcinoma. Two months later the patient died at another hospital, and autopsy confirmed the diagnosis of primary carcinoma of the liver.

CASE 22. M. G. (M.G.H. U-382144), a 46-year-old man, entered the hospital complaining of girdling pain around the abdomen, abdominal swelling, anorexia, vomiting and diarrhea. He was a moderate user of alcohol.

Physical examination disclosed a markedly distended, tense abdomen, with a fluid wave and shifting dullness in both flanks. The liver edge was palpable 7 cm. below the costal margin border; it was apparently smooth and extended across the midline into the left upper quadrant. The spleen was not palpable. Slight jaundice was present. Esophageal varices were not demonstrable by x-ray.

At the time of peritoneoscopy, 3000 cc. of slightly cloudy, yellow fluid was aspirated. The liver throughout both lobes was definitely hobnailed and thickened. On the anterior surface of the right lobe there were several yellowish areas that suggested neoplasm but were not typical. A biopsy was obtained from one of these areas, and the tissue appeared necrotic rather than malignant. Another biopsy was obtained from an area that appeared cirrhotic. The pathological report was toxic cirrhosis and hepatoma.

CASE 23. S. F. (M.G.H. U-300235), a 51-year-old man, entered the hospital with a history of having vomited about a quart of bright-red blood. He had been a known diabetic patient for 12 years. He had always used a considerable amount of alcohol. The liver was palpable two fingerbreadths below the right costal margin. The spleen was not palpable, nor was there any ascites or jaundice. Esophageal varices were not demonstrable by x-ray.

At peritoneoscopy the liver throughout both lobes showed multiple yellowish nodules, varying from 2 to 10 cm. in diameter. In fact, the liver seemed to be at least one third to one half infiltrated with tissue that looked carcinomatous. The biopsy was toxic cirrhosis with possible neoplasia.

Seven months later, the patient died at another hospital and autopsy showed toxic cirrhosis and primary carcinoma of the liver, with metastases to the portal, mesenteric and pancreatic lymph nodes.

CASE 24. D. J. C. (H.H. U-40465), a 56-year-old man, entered the Huntington Memorial Hospital because of pain in the right upper quadrant, a severe chill, vomiting and loss of weight. He had been a heavy user of alcohol, especially before Prohibition, drinking "a dozen drinks a day."

Physical examination revealed a large mass filling the entire upper abdomen, having a tender, firm, smooth edge and moving with respiration, and questionable nodular areas in the epigastrium. The spleen was not palpable. There was slight jaundice and a small amount of abdominal fluid. No esophageal varices were demonstrable by x-ray.

At peritoneoscopy the liver throughout was studded with numerous whitish yellow, umbilicated lesions, varying from 2 to 5 cm. in diameter, many of them coalescing. The right lobe of the liver was almost completely replaced with tissue that had the appearance of carcinoma. About 2000 cc. of yellow fluid was aspirated. A biopsy of the liver resulted in a diagnosis of carcinoma, unclassified. About 2 weeks later

the patient died and autopsy revealed primary bile-duct carcinoma of the liver with metastases to the periportal and peripancreatic lymph nodes.

CASE 25. L. W. H. (P.D.H. U-8211), a 72-year-old man, entered the Pratt Diagnostic Hospital complaining of pain in the right upper quadrant, nausea and vomiting, weakness and loss of weight. He had been a moderate user of alcohol all his life.

Physical examination revealed at least three distinct masses within the abdomen. The first, taken to be liver, descended with respiration about four fingerbreadths below the right costal margin. The edge was sharp and irregular and definite tender nodules were palpated along its border. Below this was a round, extremely hard mass to the right of the midline, extending approximately to the level of the umbilicus. In the right flank a round, smooth, hard, slightly nodular mass was felt below the liver. The spleen was not palpable. There was no jaundice or ascites. Esophageal varices were not demonstrable by x-ray.

Peritoneoscopy disclosed a comparatively normal left lobe of the liver, but the edge of the right lobe was markedly rounded and contained a yellow nodule 3 to 4 cm. in diameter, consistent with carcinoma. Farther in the right flank, but continuous with the liver and more posteriorly, was a hard, gray, nodular mass, consistent with carcinoma invading the liver. There was another mass occupying the right upper quadrant below the liver, apparently distinct from the liver and covered entirely by omentum. A biopsy of the mass in the right flank resulted in a diagnosis of primary liver-cell tumor.

These 5 cases of proved hepatoma present certain features of interest. All the patients were men in middle or late life. All except one had used alcohol in moderate to large amounts. The only one who denied the use of alcohol was a native-born Armenian who may have been exposed to some unusual liver disease. All except one complained of upper abdominal pain, usually in the right upper quadrant or epigastrium. Loss of weight and vomiting were noted in 3 cases.

In all cases physical examination showed an upper abdominal mass, usually of considerable size and frequently thought to be somewhat nodular. The spleen was not palpable in any case, nor were esophageal varices ever demonstrable by x-ray. Jaundice and ascites were present in 2 cases.

The biopsies obtained at peritoneoscopy were positive in 2 cases for hepatoma, in 1 case for carcinoma (unclassified), and in 1 for toxic cirrhosis with possible neoplasia. There was some difference of opinion among the pathologists in the fourth case, and it was thought that if carcinoma were present it was primary hepatoma. In the fifth case, the neoplastic areas were not demonstrable by peritoneoscopy, owing to adhesions and also to the fact that the neoplasm was within the substance of the liver.

Heretofore it has always been impossible to make a positive clinical diagnosis of primary carcinoma of the liver, but with the aid of the peritoneoscope a positive diagnosis is now possible.

DISCUSSION

Since the division of these cases into groups is obviously arbitrary, it may be as well to discuss all of them together. It is evident that peritoneoscopy

is a procedure that is of great importance and that by this method alone many doubtful clinical diagnoses can be positively established and some others entirely changed. Peritoneoscopy may be safely performed in many patients on whom one would hesitate to do a laparotomy or where a laparotomy would be too formidable a procedure for the information obtainable.

Is metastatic cancer present in the liver? Its presence or absence may change the treatment entirely. Given a large nodular mass in the epigastrium it may be assumed clinically to be cancer in the liver, but peritoneoscopy may show that the mass does not involve the liver; it may be a large carcinoma of the stomach that can be successfully resected. Conversely, a nonpalpable liver may contain metastatic cancer demonstrable by peritoneoscopy and a laparotomy may thus be avoided.

The fact that a liver is large is interesting and important, but what does it mean? Liver-function studies may show good or bad function, but still one does not know the diagnosis until a biopsy is performed. Many times I have been surprised to find cirrhosis when I suspected cancer, and vice versa; and at other times cancer is superimposed on cirrhosis. Occasionally, sarcoma is found instead of cirrhosis. Sometimes when liver disease has been suspected, peritoneoscopy has revealed a large, normal liver, ovarian carcinomatosis, hemangiosarcoma or tuberculous peritonitis. Moreover, by getting liver biopsies in cirrhosis before and after treatment, it is possible to watch the progression

or regression of the process, and thus evaluate the therapeutic procedures. The differential diagnosis of patients with ascites or jaundice, or both, is often difficult, but by direct endoscopic inspection the problem frequently is easily solved. A rare diagnosis, such as sarcoid of the liver, may occasionally be made by peritoneoscopy. Primary liver-cell carcinoma can be positively diagnosed by peritoneoscopic biopsy.

CONCLUSIONS

Peritoneoscopy is an important and well-established method of examining the peritoneal cavity that is especially applicable to the differential diagnosis of liver disease. With biopsy, a suspected diagnosis is made positive.

In a series of peritoneoscopies in 435 patients, the examination was undertaken primarily to study the liver in over two thirds of the cases. One hundred and seventy patients were found to have metastatic carcinoma, 73 had cirrhosis, and the remainder had various diseases, including hepatoma, sarcoma, lymphoma, lymphangioma, Banti's disease, cholangitis, polycystic liver, echinococcal cyst and sarcoid.

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DICUMAROL THERAPY IN THROMBOTIC EMERGENCIES*

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SINCE August, 1941, it has been the policy at the Lahey Clinic to treat thrombotic emergencies by one or more of the following three relatively new methods: paravertebral procaine sympathetic block,¹ venous section and ligation,² and anticoagulant therapy with Dicumarol, with or without heparin.³ Procaine sympathetic block is reserved for patients with thrombophlebitis (phlegmasia alba dolens) in whom swelling exists, in order to abolish constrictor reflexes, promote arteriolar pulsation, enhance oxygenation, restore normal capillary pressure, and thus reduce edema. Sympathetic block probably has no influence on the prevention of pulmonary embolism.

Because of the probable efficacy of anticoagulation therapy in the prevention of postoperative embolism, venous section and ligation are reserved for patients with phlebothrombosis who are over fifty years of age and who have had a warning benign embolism. This rule is not absolute, however, even in these cases, and the procedure has been resorted to only four times since October, 1941. So far there has been no fatality and only one recognizable recurrent benign pulmonary embolism among 46 patients with postoperative venous thromboses treated by anticoagulation therapy, all of whom were candidates, in varying degree, for pulmonary embolism. The phrase "in varying degree" is used advisedly because only 23 of these patients fell into the group with postoperative benign embolism, who are notoriously likely to develop subsequent benign or fatal emboli. We do not hesitate to employ venous section and ligation in patients with a history of multiple pulmonary emboli, postoperative or otherwise, but we advise a prolonged course of anticoagulation therapy after ligation when there is a likelihood of continuing active phlebitis and formation of venous thrombi. This is considered necessary because at autopsy venous thrombosis has been seen to extend above the point of section and ligation and to constitute the source of further pulmonary emboli, although severance of the vein was at a point above the level of the clot.

A rational use of these three methods, either singly or combined, was the subject of another paper.⁴

Anticoagulant therapy by heparin alone is expensive for the patient and tedious and laborious for the professional staff, but with the advent of Dicumarol, which can be given by mouth, there is available a cheap and easy preventive of intravascular clotting. However, heparin is now being given the first two

to five days to cover the immediate emergency period before Dicumarol has caused a fall in the prothrombin percentage.

CLINICAL USE OF DICUMAROL

The advantages of anticoagulation therapy with Dicumarol were discussed in statistical studies by Allen, Barker and Waugh.⁵ The experience at the Lahey Clinic, as outlined in this paper, corroborates their conclusions. In addition, I wish to point out the danger of hemorrhage and even death in the use of this potent hemorrhagic agent.

The isolation of Dicumarol (3,3'-methylenebis, 4-hydroxycoumarin), the active principle of spoiled sweet clover causing hemorrhagic disease of cattle, by Link and his associates⁶⁻⁹ at the Wisconsin Agricultural Experiment Station at the University of Wisconsin and the pioneer clinical work by Meyer and his associates^{10,11} and of Butt, Allen and Bollman¹² are examples of excellent pharmaceutical and clinical research. The scientific curiosity of a veterinarian, Roderick,¹³ prompted the development of this new drug after Quick¹⁴ proved that its action on the clotting mechanism is due to the lowering of the prothrombin content of the blood. Whether this action is due to the inhibition of the formation of prothrombin in the liver or in the blood stream is unknown. Butt, Allen, Bollman and Preston^{12, 15} have shown that intravascular clotting is delayed when the prothrombin time is prolonged by Dicumarol.

I have found, as have other investigators,^{5, 10-12, 15, 16, 17, 18} that Dicumarol has no consistent effect on the platelets, hemoglobin, red-cell count, white-cell count, capillary fragility, clot retraction, serum calcium or fibrinogen. The clotting time was prolonged only when the prothrombin time was reduced to low levels, usually around 40 per cent of normal.

REGULATION OF DOSAGE

After trying various doses of Dicumarol, an initial dose of 300 mg. for a patient below 120 pounds and 400 mg. for one over 120 pounds was adopted. A daily maintenance dose of 100 to 300 mg. was administered, depending on the rapidity of the fall of the prothrombin time. The average total amount required to maintain the prothrombin time below 75 per cent† was 1200 mg. in eight days. When the

*The prothrombin time is expressed in percentage of normal because the rate of clotting of the blood is directly proportional to the amount of prothrombin present, as described by Quick.¹⁴

†The thromboplastin proved to be too accurate for use in the laboratory, so the thromboplastin was diluted with saline solution.

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prothrombin time fell below 60 per cent or fell precipitously, the drug was discontinued. These doses of Dicumarol were given regardless of whether heparin was administered simultaneously. Heparin administration in itself may cause a fall of the prothrombin percentage to around 75 per cent of normal and does not necessitate stopping the Dicumarol. The administration of heparin is guided by the clotting time, Dicumarol by the prothrombin percentage.

One of the greatest difficulties in Dicumarol therapy is the determination of the amount of Dicumarol necessary to obtain the desired effect on prothrombin time. The maximum dose in this series was 3300 mg. in fourteen days, which was followed by reduction of the prothrombin time from 89 to 35 per cent. The minimum dose was 576 mg. in two days, reducing the prothrombin time from 78 to 27 per cent. The prothrombin time may continue to drop as long as five days after the drug is discontinued. Bleeding may occur with the prothrombin percentage below 40. The latent period of Dicumarol varied from one to six days. In combined heparin and Dicumarol therapy, therefore, it may be necessary to administer heparin longer than the average two-day period. Of 56 patients receiving Dicumarol, 5 who had adequate doses gave no response. Two of these were also heparin resistant. Others have noted this phenomenon in postoperative venous thrombosis, which is sometimes accompanied by a rise in platelet count and prothrombin time, and may indicate true hyperprothrombinemia. One of the patients exhibited irreversible shock and bloody pulmonary edema in spite of adequate replacement of blood loss by transfusion.

PRECAUTIONS TO BE OBSERVED

The following precautions should be observed: Dicumarol should not be given to patients with hepatic damage, especially if reduction in prothrombin percentage has already occurred. Its use is contraindicated in any case of hemorrhagic diathesis except in those cases in which it is considered certain that splenectomy will cure the condition. The morning prothrombin time should be determined before the daily afternoon dose of Dicumarol is given.

The typical course of a case under combined Dicumarol therapy and heparin is shown in Figure 1. The source of the pulmonary embolism was thought to be a pelvic phlebothrombosis following surgical resection of a carcinoma of the right ovary with side-to-side anastomosis around a carcinoma of the sigmoid. A thirty-six-hour latent period in the action of Dicumarol was evident. When heparin was discontinued, the Dicumarol effect was maintained for at least seven days. The patient was allowed to get out of bed without incident nine days after the occurrence of pulmonary embolism.

If the patient's surgical condition permits, he may sit up when the prothrombin percentage is below 70. Of this series of venous thrombotic patients, 68 per cent were out of bed without untoward incident within two weeks of recognition of the original vascular accident.

Table 1 gives the varieties of thrombotic emer-

TABLE 1. Diagnoses in 56 Cases Treated with Dicumarol Alone or Combined with Heparin.

DIAGNOSIS	No. of CASES
Postoperative venous thrombosis with pulmonary embolism . . .	23
Postoperative venous thrombosis without pulmonary embolism . .	19
Thrombophlebitis	13
Phlebothrombosis (2 with femoral ligation)	6
Venous thrombosis or embolism complicating previous operation (prophylactic)	6
Suspected pulmonary embolism (later course proved doubtful) .	1
Suspected venous thrombosis (later course proved doubtful) . .	1
Pharyngitis (after splenectomy)	1
Arterial embolism	2*
Coronary occlusion	1
Dissecting aneurysm of aorta (mistaken for pulmonary embolism)	1
Superficial phlebitis migrans	1
Thrombosis of lateral sinus and rolandic vein with right hemiplegia and partial aphasia	1
Total	56

*One of these cases is also included in "postoperative venous thrombosis without pulmonary embolism."

gencies found in the patients receiving Dicumarol either alone or combined with heparin in the nineteen-month period (August, 1941, to April, 1943).

RESULTS OF DICUMAROL THERAPY

During the nineteen-month period, 46 patients with venous thrombosis or a history of venous thrombosis were treated with Dicumarol (Table 2). Thirty

TABLE 2. Data in 46 Cases of Postoperative Venous Thrombosis.

REASON FOR ANTI-COAGULANT THERAPY	NUMBER OF CASES	SUBSEQUENT THROMBOSIS	SUBSEQUENT EMBOLISM	SUBSEQUENT FATAL EMBOLISM
Postoperative pulmonary embolism or infarction	23	0	1	0
Postoperative venous thrombosis	17*	0	0	0
Venous thrombosis or embolism complicating previous operation	6	0	1	0
Totals	46	0	2	0

*Thirteen of these patients had thrombophlebitis; the other 4 had phlebothrombosis.

of these patients also received heparin. Six of them also had paravertebral sympathetic procaine block. None had venous division and ligation.

I have divided these cases, as did Allen, Barker and Waugh⁵ at the Mayo Clinic, into three groups: postoperative pulmonary embolism or infarction, postoperative venous thrombosis, and venous thrombosis or embolism complicating previous operation. These authors compared the expected number of emboli in untreated patients with the actual number that occurred under Dicumarol therapy, their expectancy figures being those prepared by Barker and his associates.¹⁹ It is doubtful whether such

expectancy figures can be applied with accuracy to patients in another clinic with different hospital and surgical routines and under different climatic conditions. Since such expectancy figures from the Lahey Clinic have not been compiled on account of

embolism occurred. In none of the 46 patients with venous thrombosis did additional foci of thrombophlebitis or phlebothrombosis become evident once treatment was begun. Of the 40 patients in whom venous thrombosis occurred after operation,

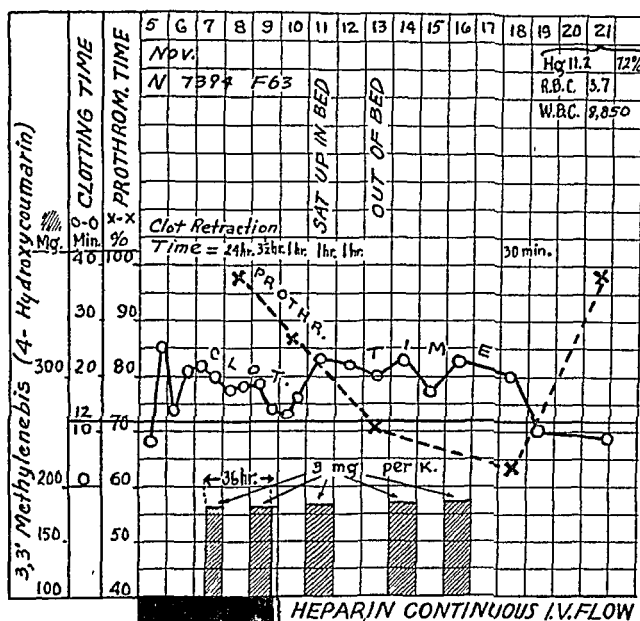


FIGURE 1. Course of a Case under Combined Dicumarol and Heparin Therapy.

the pressure of wartime work, all that can be reported is that only 1 subsequent benign and no subsequent fatal embolism were encountered in 23 patients with postoperative pulmonary embolism treated with heparin combined with Dicumarol. The embolism occurred when the prothrombin time was reduced to 55 per cent.

In 17 cases of postoperative venous thrombosis uncomplicated by embolism at the time of beginning anticoagulation therapy, no pulmonary embolism occurred. Since phlegmasia alba dolens is rarely a cause of pulmonary embolism, this group has been subdivided into 13 cases of thrombophlebitis and 4 of phlebothrombosis. All observers in this field realize that other silent foci of phlebothrombosis often occur in thrombophlebitis and give rise to pulmonary embolism, well justifying the protection of such patients. Also, my experience has shown that anticoagulation therapy greatly shortens the morbidity period from phlegmasia alba dolens.

In 6 patients with a history of thrombophlebitis or embolism following a previous operation, no

with or without pulmonary embolism, 9 were out of bed one week or less after the initial vascular accident was recognized, and 27 within two weeks.

TABLE 3. Complications in 56 Cases.

Deaths	No. or Cases	Per Cent
Directly ascribable to Dicumarol	2	4
Hemorrhage into wound, retroperitoneal tissues and mesentery, and bloody pulmonary edema	1	
Dissecting aneurysm mistaken for pulmonary embolism	1	
Hemorrhage into stomach	2	
" " " "	1	
Hemorrhages	1	
into wound (1 fatal and 1 saved by transfusion)	2	8
into stomach (fatal)	1	
Hematomas in buttock	1	
" " " "	1	
" " " "	1	
" " " "	1	
Total	12	18

Among the 46 patients with venous thrombosis no fatal pulmonary embolism occurred.

COMPLICATIONS

Of the 4 deaths occurring during Dicumarol therapy (Table 3), 2 can be attributed to hemor-

rhage, the result of lowered prothrombin content of the blood.

The first death occurred following a second-stage sympathectomy for chronic deep femoral thrombophlebitis. Venograms before and after spinal anesthesia had demonstrated a spastic element. Following the first-stage sympathectomy, Dicumarol was given successfully. The prothrombin time was allowed to return to normal before the second stage was done, after which Dicumarol was again administered. The second daily dose of the second course of Dicumarol was given before that morning's prothrombin time was determined. By the third morning the prothrombin time had dropped to 37 per cent, after 688 mg. of Dicumarol had been given in two days. The patient had signs of hemorrhage and shock, and six transfusions failed to save her life. Autopsy showed hemorrhage into the abdominal wall, retroperitoneal tissues and wound and bloody pulmonary edema.

The second death due to hemorrhage occurred in a patient with a dissecting aneurysm of the aorta, which was proved at autopsy but was mistaken during life for a postoperative pulmonary embolism. Three daily doses of Dicumarol—400, 200 and 100 mg., respectively—were given, the prothrombin time falling precipitously from 100 to 54 per cent in three days. By the fourth day, without further Dicumarol, the prothrombin time fell to 33 per cent, where it remained for the next five days, when the patient was allowed to sit up. Six days after the last dose of Dicumarol, the prothrombin time suddenly fell to 11 per cent. The only sign of hemorrhage was moderately bloody urine whose source was a transurethral resection that had been performed three weeks before. Because of the low prothrombin level, a transfusion was given, but death occurred suddenly three hours later, with blood exuding from the patient's mouth and nose. Autopsy showed petechial hemorrhages into the pericardium, a gastric mucosa oozing blood, a stomach full of blood and regurgitation of blood into the esophagus. No communication between the dissecting aneurysm and the esophagus or stomach could be found. This patient would undoubtedly have died of the dissecting aneurysm, but perhaps under other circumstances might have been saved by repeated transfusions.

The third death was due to a perforated gall bladder, and the fourth to gangrene of both legs from saddle embolism.

Table 3 gives a summary of the hemorrhagic accidents in the total series of 56 patients. Transfusion was necessary in 3 cases. There were 2 deaths directly ascribable to Dicumarol (4 per cent) and 8 cases with hemorrhage (14 per cent).

SUMMARY AND CONCLUSIONS

Fifty-six patients with thrombotic emergencies were treated by Dicumarol or Dicumarol combined

with heparin as anticoagulants, between August 1941, and April, 1943. Two deaths occurred (4 per cent), 1 of which can be attributed unequivocally to Dicumarol poisoning and hemorrhage. Hemorrhagic phenomena were evident in 8 cases (14 per cent). These complications emphasize the dangers and disadvantages of Dicumarol therapy, but the obvious advantages to date appear to outweigh the dangers of this preventive method if adequate laboratory facilities are available and proper precautions are observed.

The principal precaution to be observed is the determination of the morning prothrombin time before ordering the daily maintenance dose of Dicumarol.

The combined use of heparin and Dicumarol is considered safe only if the doses of heparin are controlled by twice-daily determinations of the coagulation time of the blood, and the doses of Dicumarol by daily determinations of the prothrombin time.

One benign and no fatal pulmonary embolism occurred in a series of 46 cases of venous thrombosis treated by the anticoagulant Dicumarol, alone combined with heparin.

This series of 46 cases of thrombophlebitis is large enough to draw the conclusion that venous ligation is an unnecessary procedure. If a patient over fifty and has had a warning benign pulmonary embolism, therefore, venous ligation is still indicated. If statistical proof can be accumulated from other workers in this field, venous ligation may prove unnecessary except in rare cases of recurrent embolism occurring in spite of anticoagulation therapy.

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ABSCESS OF THE SPLEEN*

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ABSCESS of the spleen has attracted little attention in the American literature. Although excellent reviews and case reports have been published by Elting,¹ Inlow,² Billings,³ and Walker⁴ and recently by Lemmon and Paschal,⁵ the European literature on the subject is much more extensive. This is unfortunate, for, although splenic abscess is not of frequent occurrence, its diagnosis is not difficult when kept in mind. Furthermore, the correct therapeutic approach greatly reduces an extremely high mortality rate (80 to 100 per cent.^{2, 5, 6, 7}) It would be most unfortunate, therefore, if the diagnosis were missed simply because the possibility had not been considered. Splenic abscess occurred in 0.4 per cent of autopsies at the Boston City Hospital, according to Walker,⁴ and Billings³ reported 24 cases in 3600 autopsies, an incidence of 0.7 per cent.

The classification of splenic abscesses has been simplified since Kuttner⁷ outlined seven varieties in his classic paper on the subject. Three major modes of pathogenesis are now generally recognized.

Traumatic abscesses constitute an estimated 15 per cent of all splenic abscesses. Clinically they result from trauma to the organ, with a resultant perisplenic hematoma. Under such conditions, the hematoma forms a point of lessened resistance, and is subject to suppuration whenever there occurs a bacteremia resulting from major or minor infective processes. Experimentally, splenic abscesses have been produced by Caldarera,⁸ who rendered animals' spleens susceptible by traumatizing them and injected *Staphylococcus aureus*. Kuttner⁷ similarly produced abscesses of the spleen. In 1927, Inlow reviewed 23 cases of traumatic abscess and discussed one of his own. He found that conservative treatment of these cases resulted in a mortality of 100 per cent, whereas with surgical intervention this figure was reduced to 38 per cent.

Abscess of the spleen occasionally results from extension of a neighboring pathologic process. Thus, infected colonic or gastric neoplasms may invade the spleen, or left subphrenic collections may erode into it so that the organ forms the floor of the abscess cavity. In a case seen at the Mount Sinai Hospital,

a large abscess was found in a spleen invaded by lymphosarcomatous tissue. Most such cases are of only academic interest, since the patient is usually suffering from a serious condition to which the splenic abscess is secondary and drainage of the abscess would be of no therapeutic benefit.

The most important group of splenic abscesses are those resulting from metastatic spread of infection elsewhere. Thus, furunculosis, erysipelas, otitis media, and femoral thrombophlebitis, as well as appendicitis and salpingitis, have preceded development of abscess of the spleen. It is important to divide this group into those cases in which the infection spreads along venous channels, and those in which the infection reaches the spleen through the splenic artery. Cases in the first group, which includes the case presented below, usually result from intra-abdominal suppuration. Cases that come to autopsy usually show pyelophlebitis and thrombophlebitis of the splenic vein. Thus, Faunteroy⁹ reported a case following acute appendicitis in which autopsy revealed three splenic abscesses with thrombosis of the splenic vein and with numerous small necrotic areas in the liver. Cooke¹⁰ found a large and septic spleen with purulent thrombophlebitis of the mesenteric and splenic veins resulting from a perforated colonic diverticulum. Such cases tend to have a serious prognosis because of the associated venous lesions.

The large number of cases resulting from suppuration elsewhere are probably due to spread of infection by way of the splenic artery. In this group must belong Walker's⁴ case, with streptococcal sepsis resulting from thrombosis of the lateral sinus secondary to mastoiditis; Billings's³ case, in which *Staph. aureus* was cultured from a recently incised carbuncle of the neck as well as from the splenic abscess; Cutler's¹¹ case, which was preceded by otitis media; Eliason's¹² case, in which a staphylococcal sepsis and splenic abscess followed a peritonitis; and the case of Lemmon and Paschal,⁵ in which a splenic abscess was preceded by thrombophlebitis of the femoral vein. In these cases, it is apparent that the infecting material must have traversed the lesser circulation and escaped the pulmonary network in order to reach the spleen. The only alternative pathway is through a congenital

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cardiac defect. In most cases, however, no cardiac murmurs indicative of such a lesion are described.

Special mention should be made of the group of cases described by Rabin and Moolten.¹³ These observers reported 5 cases of lung abscess from which splenic abscess developed—presumably by way of the splenic artery. In each case, infection of a branch of the splenic vein occurred at the site of the abscess and eventually resulted in fatal pylephlebitis.

Metastatic splenic abscess may develop clinical manifestations from one day to several months after the appearance of the primary source. The onset is often heralded by sudden severe pain in the left hypochondrium, although the pain may also be of gradual onset. On the other hand, when a large abscess is buried in the middle of the spleen, there may be no pain referred to the splenic region, as in Fauntleroy's⁹ case. It is usually stated that abscesses of the upper pole of the spleen give rise to pleuritic pain, with inspiratory increase of the pain and occasional radiation to the left shoulder, whereas abscesses of the lower pole give rise to peritoneal signs. In general, this is true, but it should be noted that in May's¹⁴ case a superior pole abscess ruptured into the peritoneal cavity. Accompanying the pain are the general symptoms of severe infection—temperature, usually spiking, chills and leukocytosis. The temperature generally reaches 103°F. or more, but in Lemmon and Paschal's⁵ case it remained below 100 before drainage of the abscess. Similarly, the white count may reach 20,000 to 30,000 but in several cases has been below 10,000. It is apparent, therefore, that splenic abscess should be suspected in any patient with pain in the left upper quadrant of the abdomen, especially if an adequate previous focus of infection is found or if there are any symptoms or signs of sepsis.

Physical examination usually discloses tenderness and spasticity in the left upper quadrant, and careful observation may reveal edema of the soft parts overlying the spleen and even a tense, glistening skin. The spleen is almost always enlarged, and is usually felt clinically. There may be signs of fluid in the left pleural cavity, and radiologic examination may disclose this, with or without elevation of the left leaf of the diaphragm.

Splenic puncture as a diagnostic measure has been both supported and condemned. The procedure is obviously not without danger. In doubtful cases, however, it is useful. The safest policy is to restrict its use to such cases and to have the puncture performed in the operating room, with all preparations made for splenotomy or splenectomy. If pus is aspirated, the needle should be left in place until the spleen is exposed. In this way, the danger of producing empyema by introducing pus along the track of the needle is obviated.

If untreated, splenic abscesses run a severe septic course. A few become chronic, with sterile pus, and

produce few symptoms. The overwhelming majority, however, rapidly go on to a fatal termination if surgical intervention is not instituted. The procedure employed may be splenectomy or splenotomy. Splenotomy is usually preferred unless the organ is easily mobilizable and free of adhesions, when splenectomy may be indicated. Of 55 cases gathered by Billings,³ splenotomies were performed in 51, with 7 deaths, and splenectomies in 4, with 3 deaths. Splenotomy may be performed through a transpleural, transperitoneal or retroperitoneal approach. This varies with the site of the abscess, as well as with the preference of the surgeon.

In those cases in which suppuration is localized in the spleen, surgical intervention produces a cure in the majority. Operation is contraindicated in cases of splenic abscess resulting from subacute bacterial endocarditis, in which the prognosis is necessarily the grave one of the underlying disease. Similarly, surgery cannot offer much hope when the abscess is secondary to extensive pyemia with multiple suppuration elsewhere, for in such cases the splenic lesion is an incidental and unimportant finding. When the splenic abscess is the result of, or causes, suppurative splenic and portal thrombophlebitis, the prognosis is usually grave, but surgery offers the patient a slight chance, especially if splenectomy with ligation of the purulent vein can be performed. Such a case, with an unsuccessful result, is reported below.

Of 30 cases of splenic abscess described by Walker¹ from autopsy material, 22 had abscesses involving other organs, leaving only 8 that could be benefited by surgery. Since this series included only cases seen at autopsy, patients diagnosed clinically as splenic abscess have a higher percentage of operability.

CASE REPORT

A 27-year-old woman bookkeeper (501064), was admitted to the Mount Sinai Hospital on January 30, 1943. Six weeks before admission, she had an appendectomy with drainage at another hospital, because of a 2-weeks' illness characterized by abdominal pain, fever and pharyngitis. The removed appendix was reported as showing periappendicitis. Three weeks postoperatively, the patient was discharged well, but on the same day she developed shaking chills, fever up to 105°F. and sweats. One week after discharge she returned to the hospital, where she continued to have high fever and sweats, without localizing symptoms. After 2 weeks she was transferred to the Mount Sinai Hospital.

Physical examination on admission revealed an acutely ill woman. The temperature was 105.0°F., the pulse 130, the respirations 30, and the blood pressure 110/58. The eyes, ears, nose and throat were normal. Examination of the lungs disclosed an impaired percussion note and diminished breath sounds at the left base. There were no rales. The heart was not enlarged. There was a short systolic murmur at the apex, and embryocardiac rhythm was noted. In the right lower quadrant of the abdomen was a wound draining a minimal amount of mucopurulent material. The liver was barely palpable, and under the left costal cage a definite tender mass was felt. Both costovertebral angles were tender, and there was a suggestion of a bulge on the left. The white-cell count on admission was 30,000, with 95 per cent neutrophils. The urine showed a trace of albumin and a few granular and cellular casts. A blood culture taken on admission was later re-

ported as positive for beta-hemolytic streptococcus. X-ray examination of the chest showed a small amount of fluid in the lower portion of the left pleural cavity. There was no elevation of the diaphragm.

The day after admission, the left side of the chest was tapped. The 10th interspace was entered at one third of the distance from the posterior axillary line to the spine. Superficially, after penetration for a short distance, thin sanguinous fluid was obtained. The needle was inserted deeper, and at a depth of 5 cm. pure pus was obtained, from which beta-hemolytic streptococci were grown. The patient was therefore removed to the operating room.

The report of the surgeon (Dr. Harold Neuhoef) follows:

Aspiration at the level of the 10th interspace revealed pus. The needle was left in place and the 11th interspace was aspirated. Here sanguinous fluid was obtained. A preoperative diagnosis of splenic abscess with rupture of the spleen was made.

Accordingly, the 11th rib was liberally excised. The pleural cavity, which was free of fluid but potentially infected by aspiration, was traversed and an upward bulge of the diaphragm toward the midline was noted. General anesthesia was administered, local anesthesia having been employed up to this point. The diaphragm was sutured to the margins of the thoracic wound and was then incised, its edges being pulled up to the surface and sutured over the first layer in order to shut off completely the free pleura. This was achieved down to the posterior part of the wound, at which place a tube was inserted for drainage of the potentially infected pleura. The collection of pus was opened up and was found to be partly within and partly outside of the spleen. The latter was found to be split in two. There was then evacuated a considerable collection of old fluid blood from beneath the diaphragm, situated more medially than the collection of pus. The abscess cavity was packed.

The subphrenic space itself was lightly sealed off by adhesions between the spleen and abscess wall on one side and the undersurface of the diaphragm on the other side. Thus there was no true subphrenic abscess.

Postoperatively, the patient showed no improvement. The temperature continued to range from 102.4 to 106°F. despite blood transfusions and the administration of sulfathiazole. On the 2nd day the patient became confused and disoriented. She continued to run a septic downhill course and died 3 days postoperatively.

Autopsy (12407). The relevant findings at the autopsy performed by Dr. L. Strauss, were reported as follows:

The spleen is enlarged, weighing 380 gm. At its upper pole there are two large irregular defects, one on the anterior surface, the other on the posterior surface underneath the adherent diaphragm. In the vicinity of these defects, the capsule shows irregular, yellowish-gray discoloration, over the remainder of the organ it is smooth and of normal color — purplish gray. On section, a huge, multiloculated abscess is found, involving about half the spleen. It is lined by ragged, necrotic tissue and filled with blood clots. The lower half of the spleen is soft and shows abundant bright-red pulp and distinct follicles. The splenic artery shows no change.

From the portal spaces thick, yellow pus exudes in many areas throughout the liver. The portal vein is thickened, and its lumen contains adherent membranous

fibrinous material and frank pus. Pus also wells up from many of its intrahepatic branches. At the point of junction of the superior mesenteric and splenic veins and in the splenic vein, slightly adherent fibrinous thrombi are encountered.

The right tube is thickened and hyperemic, and its fibrinated end is closed. In the cul-de-sac, irregular, raised yellow patches are seen on the serosa.

The small intestine does not show noteworthy changes except for the lower part of the ileum, where numerous fibrous bands are found connecting various loops. There is grayish discoloration of the serosa, which is irregularly thickened over the mesentery. Small yellow patches are found on the mesentery near the insertion of the bowel. The branches of the superior mesenteric veins are not involved by the thrombotic process. The cecum is adherent to the ileum; the appendix has been removed.

Anatomical diagnoses: purulent thrombophlebitis of the portal and splenic veins; left subphrenic and splenic abscess; chronic mesenteritis and localized peritonitis of the ileocecal region; chronic right salpingitis; and chronic peritonitis of the cul-de-sac.

SUMMARY

Splenic abscess is an infrequent but not rare condition. Its diagnosis is not difficult when it is kept in mind. A patient who develops symptoms and signs of a lesion in the left upper abdomen and who has a recent history of even minor suppuration elsewhere should be explored and splenotomy or splenectomy performed.

A case of splenic abscess is reported that had its origin in a diffuse inflammatory process of the pelvic peritoneum. The abscess was accompanied by a pyelephlebitis and a thrombophlebitis of the splenic vein that led to a fatal outcome, despite surgical intervention.

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MEDICAL PROGRESS

SYPHILIS (Concluded)

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CLINICAL PROBLEMS

Syphilis in Blood Donors

A study of the method of handling blood donors found to have a positive or doubtful reaction for syphilis has been made by Frye, Keller and Kampmeier.³⁶ A geographically representative group of 603 hospitals replied to a questionnaire sent out by these authors. Of these institutions, 6.5 per cent were not testing blood donors for syphilis, small hospitals predominating. Among the hospitals testing donors, 12.5 per cent had no definite system for notifying these donors when they were found to have a positive or doubtful reaction for syphilis. Of all the hospitals, 16.2 per cent either did not examine donors for syphilis or did not notify them when the serologic test was positive. These findings indicate the need in many hospitals of more definite plans whereby the donors will be given blood tests and will be notified concerning the results. The present situation seems most deplorable. It could be construed as a grave reflection on hospital authorities, especially in view of the intense campaign to control syphilis. Financial considerations are, of course, sometimes strong deterrents, but surely it should not be too much to expect even the smallest institutions to send blood specimens to their state laboratories. One could even conceive of a malpractice suit arising on the basis of negligence should transfusion syphilis occur, or should an untested donor develop crippling lesions within a reasonable period of time.

False-Positive Serologic Reactions following Smallpox Vaccination

A reference to the phenomenon of false-positive serologic reactions following smallpox vaccination was given in a previous progress report on syphilis in this journal.³⁷ It seems of sufficient importance to warrant mentioning confirmatory data. Lubitz³⁸ observed 13 of 100 patients who exhibited positive serologic reactions for syphilis following a primary take with smallpox vaccination. All these cases had been serologically negative within a few months previously. Infectious mononucleosis was ruled out by a heterophile antibody test in the serums from 10 cases. The Kahn verification test gave no conclusive

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evidence that these were false-positive reactions. Twelve of the patients could be followed, and their serums gradually became negative. The author states that a positive serologic test may be found as late as the fifth month following vaccination.

Syphilitic Spondylitis

A report by Freedman and Meschan³⁹ seems of interest because syphilitic spondylitis, although not common, can be so easily confused with other conditions. The authors point out the difference between syphilitic spondylitis and Charcot's spine. There seems to be a marked predilection for involvement of the cervical vertebrae in syphilitic spondylitis, possibly because of more likely exposure to slight trauma and pressure. The condition may occur in congenital syphilis or during the second or third stage of acquired syphilis. There is localized pain, which may be more marked at night, stiffness and tenderness to palpation. The normal lordosis of the spinal column is offset. The head is held stiff and motion is avoided. Coexisting osseous lesions are common. To substantiate a diagnosis, active syphilis should be demonstrable and there should be rapid improvement under antisypilitic treatment. Tuberculosis of the spine may be confusing, and the two conditions may coexist. In the majority of cases the vertebrae become surrounded by more or less spur formation, imitating roentgenographically the appearance of a nonsyphilitic inflammatory spondylitis.

Neurosyphilis

The interpretation of spinal-fluid reports is often a source of concern to general practitioners, and a discussion of this subject by Rose⁴⁰ is instructive. The point is made that cerebrospinal-fluid examination is essential in establishing the diagnosis of neurosyphilis, as well as in establishing the base line for future guidance. The initial findings do not, of course, indicate the prognosis. The several spinal-fluid findings in the various types of neurosyphilis are reviewed, and the significance of component parts of the reports is explained. Rose believes that the reversal of a positive spinal-fluid reaction to negative with a year or less of treatment is strong evidence against a diagnosis of general paresis, irrespective of clinical symptoms. Repeated examinations of the spinal fluid are considered essential for guidance and adequate therapy. This author states that the cell

count and the level of total protein are of much greater importance regarding prognosis and therapy than is the Wassermann test or the gold-sol curve. It is postulated that a spinal fluid that remains strongly positive in all elements for a year or more after the institution of therapy shows that some other form of treatment should be considered. Most syphilotherapists are somewhat less conservative in this respect. In asymptomatic neurosyphilis six months of routine therapy with trivalent arsenic and bismuth is usually considered sufficient trial, complementary methods of therapy being instituted at the end of this time if the spinal fluid is not improved. In the various forms of symptomatic neurosyphilis it may be necessary to use more drastic forms of therapy within a few weeks or months if symptomatic progression is not retarded.

In view of widespread, and in some instances alarming, epidemics of anterior poliomyelitis within the last year, an article by Barker⁴¹ seems timely. A case exhibiting an acute syphilitic anterior poliomyelopathic syndrome was reported. Although this picture is seldom seen, syphilis has been reported in a small number of cases as responsible for the origin of the syndrome of anterior poliomyelitis. Barker's patient was thirty-nine years old, and a diagnosis of acute anterior poliomyelitis was made on admission to the hospital. Laboratory tests showed strongly positive Wassermann reactions of the blood and cerebrospinal fluid. The case was observed in March, which is an untimely month for acute anterior poliomyelitis. There were absence of pain and a peculiar distribution of paralysis, inability to swallow existing in conjunction with weakness of both legs. Five days after admission the patient became unable to void urine. Under intensive anti-syphilitic therapy with bismuth, arsenic and potassium iodide, improvement was rapid, and within two months the symptoms had almost disappeared. The lesson in this situation seems obvious. Intensive anti-syphilitic treatment under such circumstances may prevent changes in the spinal cord that are not already irreparable from becoming so, by the restitution of better circulatory conditions in the cord through regression of the vascular syphilitic progress.

Trauma has long been implicated as a contributory factor in the development of many lesions of syphilis. Ample evidence in favor of this belief has been found from time to time. Merritt and Solomon⁴² present further substantiation of the role of trauma in the production or exaggeration of symptoms in the various types of neurosyphilis. It is stated that a causal relation between head trauma and the development of parietic symptoms may be established within six weeks of the trauma and perhaps as long as two to three years after it. The relation of trauma to syphilitic arthropathies affords less opportunity for divergence. It is generally accepted today that Charcot's joints develop as a result of lessened sensitivity in the joints that allows repeated minor

trauma to occur without protection by the muscles or the tendons. There is less evidence of the effect of injury in other types of neurosyphilis. The one proved fact is that neurosyphilis is due to invasion of the nervous system by a spirochete. The deleterious effect of trauma on the pathologic process of neurosyphilis can only be deduced. There is divergence of opinion about the severity of trauma necessary and the time interval that must elapse between the injury and the appearance of symptoms.

In a review of tabetic arthropathies, Steindler, Williams and Puig-Guri⁴³ analyze the findings in 134 cases in which there were two hundred and fourteen Charcot's joints. A definite picture of tabes was present in only 57 of these cases. The age limits were from seventeen to eighty-two years. Of these patients 97 per cent were men. Various injuries preceded the onset of arthropathy in 59 cases (44 per cent). The time interval between the acquisition of syphilis and the onset of joint symptoms varied between five and ten years. These cases were analyzed from numerous aspects for statistical purposes. There were only 5 cases in which the joints of the upper extremities were involved. The knee was the most frequently affected joint (51 per cent of all joints, or 64 per cent of the 134 patients). Ten cases became complicated with pyogenic infection through ulcers and local sores, and all but 2 of these came to amputation. These authors believe that trauma is never the cause of syphilitic arthropathy but is undoubtedly of contributing importance in its development. It is pointed out that normal fractures may occur in a tabetic patient or in one suffering from syringomyelia, and may be produced by a perfectly adequate and plausible traumatic event.

CONGENITAL SYPHILIS

An interesting point of differential diagnosis has been discussed by Henderson.⁴⁴ Over a five-year period he observed 53 infants with erythroblastosis. Ten were stillborn, 24 died, and 19 recovered. Autopsies were performed on all 34 fatal cases. Henderson points out that the two severest forms of erythroblastosis, hydrops fetalis and hepatic cirrhosis, occur in connection with intrauterine death and are usually mistaken for congenital syphilis. A large, pale placenta occurs in both these diseases. Uncertainty will seldom arise if certain points are considered in all doubtful cases. The occurrence of a proved case in an older sibling makes the diagnosis almost certain. Congenital syphilis becomes progressively less severe in each succeeding pregnancy; in erythroblastosis the trend is opposite. The frequency and degree of prematurity are much higher in syphilitic infants than in those with erythroblastosis. The gross appearance of the placenta may be strikingly similar, but syphilitic placentas usually show areas of infarction. Osseous manifestations are absent in erythroblastosis. The

demonstration of *Treponema pallidum* in the tissues of the fetus, cord or placenta dispels doubt; it can often be found by immediate scrapings of the intima of the umbilical vein. Microscopical examination of tissue is, of course, of great assistance, but occasions some delay.

For practical purposes it is generally considered that one can disregard the possibility of cardiovascular syphilis in congenital cases. An exhaustive review of this problem has been published by Hinrichsen.⁴⁵ The literature has been painstakingly searched, and reported cases are discussed. Hinrichsen found reports of various types of vascular syphilis, with the exception of valvular heart lesions. Although congenital syphilitic aortitis, with or without aneurysm, has been reported, this author found no case on record with syphilitic valvular lesions of the heart. Congenital syphilitic myocarditis of interstitial and nodular types has been described but its incidence is uncertain. Autopsies on stillborn or early post-natal fatalities are almost the only cases recorded. The role of syphilis in the production of congenital malformations of the heart has not been determined. Congenital syphilis as a cause of hemorrhagic disease of the newborn is also mentioned in this paper.

A study of the possible effect of bismuth on the growth of children has been made by Russin, Stadler and Jeans.⁴⁶ It is reasonable to assume that there may be interference with growth, since the abnormal changes observed roentgenographically after the administration of bismuth appear at the sites of provisional ossification of growing long bones. These authors followed 10 children under treatment for congenital syphilis for periods as long as ten years. Their actual heights were compared periodically, with the predicted height, and the average difference in most cases was practically zero. The conclusion was drawn that, although the roentgenographic changes observed represent abnormalities of bone growth, the prolonged administration of bismuth does not interfere with the rate of linear growth.

The intramuscular method of administration of Mapharsen has been utilized by Astrachan and Cornell⁴⁷ in congenital syphilis. Sixty-eight patients with various stages of congenital syphilis, as well as 19 with latent acquired syphilis, were treated. Most of those with early congenital syphilis were treated by the intramuscular route, and the rest intravenously. The majority of the patients tolerated well the intramuscular injections of Mapharsen and showed no untoward reactions. Clinical and serologic results were satisfactory. These authors believe that the concurrent administration of Mapharsen and bismuth is often valuable in late congenital syphilis. They think that 0.75 mg. per kilogram of body weight should be the maximum dosage for any patient with congenital syphilis.

Levin, Hoffman, Koransky, Richter and Gumbiner⁴⁸ have applied the principles of massive therapy

to the treatment of syphilis in infants and children. Thirty-two cases of congenital syphilis and 4 in children with the acquired disease were given the five-day treatment with Mapharsen. The authors properly stress the importance of adequate pediatric care during this procedure. No serious toxic reactions or deaths occurred. The 4 cases of acquired infection promptly became seronegative; the congenital cases were notably inferior in response when compared to those of early acquired syphilis in adults. This led the authors to believe that congenital syphilis produces widespread changes more resistant to treatment than acquired syphilis. In considering this, one would hardly expect anything else unless only selected cases of early congenital syphilis in children (from birth to the age of six months) were treated. Otherwise, they would not be comparable to those of early syphilis in adults.

THERAPY

Penicillin

At the seventy-second annual meeting of the American Public Health Association, Mahoney, Arnold and Harris⁴⁹ reported favorable results in the treatment of 4 cases of early syphilis exclusively with penicillin. Each received 1,200,000 units of the drug in eight days. Dark-field examinations became negative about seven hours after the treatment was begun. Lesions were healed within two weeks. Serologic tests for syphilis became negative within thirty days. At the time of this writing, these patients had remained negative for approximately eight months. This is indeed a most startling report, and certainly one may hope for a great advance with the use of such a remarkable drug. As often before mentioned, however, caution must be exerted in predicting any results with new treatment for syphilis. It will take several years to determine whether penicillin is generally indicated in this disease. It may take ten or more years to tell whether its results are lasting. Dr. Mahoney himself, in reading this paper, urged caution in interpreting results. It is to be remembered that penicillin is not available for general use and that only a limited amount can be spared for the study of syphilis at this time.

Other Drugs

Trisodarsen. A résumé of eight years' experience with Trisodarsen has been published by Beerman, Pariser and Gordon.⁵⁰ The results of treatment of 550 patients in various stages of syphilis were analyzed. Forty-four per cent had reactions, although the majority of them were mild. Infectious and serologic relapses occurred in 10 per cent of 177 patients with early syphilis. This compared favorably with the Co-operative Clinical Group statistics of 10.1 per cent. In all other respects the results were comparable to those expected with drugs in common use, but the authors state that their patients have not been observed long enough to

valuate definitely the probabilities of cure of syphilis from this drug, although the trend appears to be favorable. The main drawback seems to be an apparent tendency of this compound to induce dermatitis.

Phenarsine hydrochloride. Two preliminary reports have appeared on the treatment of syphilis with phenarsine hydrochloride. Long⁵¹ subjected 96 patients to treatment with this drug. It was administered in a standardized manner, with bismuth in alternate series. Open lesions were rapidly sterilized, and healed satisfactorily. There was no case of relapse. The rapidity of serologic reversal was on the whole satisfactory. There was a low incidence of abnormal spinal fluids among the patients with early syphilis. The drug was well tolerated in late syphilis and the response was good. Guy, Goldmann and Gannon⁵² have also used phenarsine hydrochloride. These investigators worked out data on toxicity and cures in rats according to standard procedures. The results did not differ materially from those obtained with Mapharsen. Two hundred and thirty-three patients were subsequently treated by a standard continuous program with alternate courses of bismuth. The results were comparable to those of Long.⁵¹ Guy, Goldmann and Gannon also believe that phenarsine hydrochloride compares favorably with other drugs that are now in general use and think that it may prove more stable. Forty milligrams of the drug was administered daily for twenty-five successive days to a woman patient. The secondary cutaneous lesions disappeared at the end of ten days, and the patient tolerated the drug without any ill effects.

Clorarsen. Clorarsen has been used in the treatment of syphilis by Kampmeier and Henning.⁵³ Two hundred and fifty patients with early syphilis were treated, with satisfactory response in all respects. A standard continuous program, with alternating courses of bismuth, was employed. A single therapeutic dose produced dark-field negativity within twenty-four hours in 42 of the 45 infectious cases. No serious untoward reactions were encountered. The drug was used often without reaction in patients who had had difficulty with other arsenical preparations. The experimental use of clorarsen seems to indicate that it is effective in acute syphilis, is attended by few reactions, and may be used as an alternate drug in patients who have had reactions to other arsenical drugs.

Bismarsen. A review of fourteen years' experience with Bismarsen has been published by Beerman, Shaffer and Livingood.⁵⁴ Eight hundred and twenty-three syphilitic patients were treated with the drug during this time. All stages of the disease were included. The authors state that Bismarsen is a relatively nontoxic drug. It was frequently used in treating patients who had had unfavorable reactions to other arsenicals. This experience seems to be at variance with that of other syphilotherapists.

Perhaps more statistical study would prove these authors correct, but it seems to be a common impression that patients intolerant to intravenous arsenotherapy are more likely to develop reactions when Bismarsen is administered. Beerman, Shaffer and Livingood found that the lesions of early syphilis healed more slowly under Bismarsen therapy than under other arsenicals and that its spirillicidal action was slower. They consider it a safe and effective drug for the treatment of cardiovascular syphilis. The action of Bismarsen was found to be too slow for use against interstitial keratitis. The authors believe that it is not the drug of choice for neurosyphilis, but that for persons for whom fever therapy and other forms of chemotherapy are contraindicated it is a useful substitute. One would be justified in thinking that Bismarsen is not the drug of choice but a secondary measure primarily suitable for those in whom intravenous therapy is not feasible.

Bismuth. Two additional reports have appeared concerning the tempering effect of bismuth on therapeutic malaria. This phenomenon was mentioned in a previous progress report.⁵⁵ Thio-Bismol is the preparation employed. It has proved extremely useful in the hands of Whelen and Shute.⁵⁶ These authors found that an injection of 0.2 gm. of Thio-Bismol was effective in stopping malarial paroxysms for forty-eight hours, the drug having a selective action on alternate cycles of benign tertian malaria during the developed stage. If administered during the incubation period the drug did not appear to have any effect on the time of onset or type of fever. Proper use of this procedure can extend the range of cases that can be treated and may be of great assistance in certain emergencies. Young, McLendon and Smarr⁵⁷ have had similar experience with Thio-Bismol. These authors found that the inhibitory effect against *Plasmodium vivax* was most marked when the parasites were half grown — that is, sixteen to twenty-four hours after the last paroxysm. Older or younger parasites might not be affected at all. Other species, such as *P. malariae* and *P. falciparum*, were uninfluenced by Thio-Bismol. For the termination of *P. vivax* infections, these authors found that one injection of the drug, given on the day quinine was started, usually acted more quickly than did quinine alone by preventing a paroxysm the following day.

The importance of oral hygiene during bismuth therapy has long been known. It is a prophylactic measure that serves to ward off oral complications that may be most disturbing. Dean⁵⁸ has published a report that serves to emphasize this fact. A dark line on the gums, bleeding of the gums, excessive salivation, a bad odor of the breath, puffing and swelling of the gum tissue and an occasional loosening of the teeth were found to be remarkably improved by mouth care in the hands of dental clinics. Test cases were developed by giving general dental

care to half the lower jaw of patients showing symptoms of bismuth stomatitis. The other half of the lower jaw was not treated. There is much that the patient can do at home in the way of general mouth hygiene, gum massage and so forth. Analysis of the black deposit at the gingival margins indicates that it is probably bismuth sulfide. Dean believes that it is not necessary to interrupt or discontinue the use of bismuth treatment if adequate dental service is given before or during the periods of injection. These are well-known facts, but repetition seems worth while at this time. Dean's procedure in treating only half of one jaw provided an unquestionably satisfactory control.

Intensive Therapy

Although complications were frequent and comparatively serious with earlier attempts at massive therapy, gradual improvement and modifications of technic have slowly created a more favorable situation. Eagle and Hogan⁵⁹ have approached this problem from the experimental standpoint through a study of toxicity and excretion of Mapharsen in rabbits. Various programs of multiple injections and intravenous-drip administration were used. It was found that the total amount of Mapharsen tolerated by the animals is apparently without limit, with suitable prolongation of the treatment period. It was found possible by increasing the frequency of injections to increase significantly the amount of Mapharsen that can be administered with safety within a given period. In a continuation of this study, Eagle and Hogan⁶⁰ worked out the therapeutic efficiency and margin of safety of Mapharsen in the treatment of rabbit syphilis. The curative dose of the drug was largely unaffected by the method of administration. Multiple-syringe techniques were more effective than intravenous drip procedures. The margin of safety between the toxic and therapeutic dose could be increased by appropriate prolongation of the treatment period. An appreciable condensation of treatment beyond that permitted by triweekly, daily or multiple daily injections can be accomplished only at the cost of safety by an arbitrary decrease in the total number of injections. In a third article of this series Eagle and Hogan⁶¹ discuss the clinical implication of their experimental work. An optimal treatment schedule was worked out for the management of early syphilis in the human being. This was based on the experimental animal data and published reports on the treatment of human syphilis. Without exception, and despite the reservations that must be applied to a chemotherapeutic index based on a toxicity study in animals, the observed incidence of serious toxic reactions and death has varied inversely with the calculated margin of safety. A triweekly schedule of Mapharsen injections was worked out as having a satisfactory margin of safety. Dosage was calculated on a body-weight basis (1 mg. per kilogram), and

treatment was continued for a period of four to twelve weeks. The four-week schedule proved inadequate, as was predicted. The other schedules were continued. Approximately half the patients received weekly injections of bismuth to determine to what extent that drug would modify the end results. More than eighty marine hospital and university, municipal and state health-department clinics are now co-operating in this study. At the time of Eagle's report 2500 patients had been treated. The detailed analysis of the initial results will be described in a later paper. Another observer, Shaffer⁶² has evaluated the published reports on massive therapy from a clinical standpoint. He believes that intensive methods of treatment should still be considered experimental, and warns against the attempted use of such procedures by physicians without extensive experience. As further information is accumulated, it is expected that the experience of well-controlled work will permit the establishment of a definite procedure to be recommended in the not too distant future for use in private practice. Intensive therapy in various types of latent and late syphilis is far behind that of early syphilis. I cannot agree too heartily with Shaffer's opinions.

Combined Fever and Chemotherapy

In last year's progress report⁶³ attention was called to promising results with the use of a single artificial-fever treatment combined with chemotherapy in one intensive session for early syphilis. A subsequent report by the same authors, Thomas, Wexler, Shur, and Goldring,⁶⁴ described a serious renal complication. Forty-eight patients were treated under a two-day schedule consisting of two intravenous injections of Mapharsen on the first day, followed on the second day by two more with seven hours of artificially induced fever. Four of these patients developed acute nephrosis and 4 others severe albuminuria, together with azotemia of brief duration. All eight recovered from the acute episode. The cases were described in detail and were doubtless extremely alarming. The authors believe that the complication in these patients was an acute nephrosis induced by the combination of arsenic and prolonged use of artificial fever. This emphasizes the caution required in evaluating the safety of heroic experimental treatment of syphilis.

REACTIONS TO THERAPY

Hepatitis

Jaundice occurring during the course of anti-syphilitic therapy has been a source of concern to a great many observers. Two series of cases reported within the last year seem of interest. Kulchar and Reynolds⁶⁵ have published a survey of 144 cases. They postulate the usual causes of jaundice as intercurrent infection, arsenic intoxication or hepatorecurrence. Their cases occurred among 1032

syphilitic prison inmates, the incidence being rather high (13.9 per cent). Kulchar and Reynolds were studying hepatitis primarily from the standpoint whether bismuth was the etiologic agent, but only 3 of their cases had been treated with bismuth alone; 3 followed within four to eight weeks after the termination of arsenical therapy, and 56 within eight or more weeks. Treatment was subsequently resumed in 107 patients, 9 of whom developed a second attack of jaundice. In 4 of these cases the attack followed bismuth, and in 5 arsenic. These authors believe that previous arsenical therapy, diet, alcohol and intercurrent infection may predispose the patient to liver damage from the administration of bismuth. In other words, a summation effect of several factors, all individually unable to produce hepatitis, is proposed. Bismuth is thus placed in the role of precipitating the attack of jaundice. In the end, however, Kulchar and Reynolds favored the preceding arsenotherapy as of considerable importance. Syphilotherapists in general might question the frequency of a precipitating effect of bismuth in jaundice. It cannot be denied, however, that bismuth may create some liver damage or that it could be the last straw, so to speak, in the face of pre-existing liver damage. Ottenberg and Spiegel⁶⁶ have written on the present status of nonspecific jaundice due to infectious and chemical agents. They think that disease of the hepatic parenchyma may be due directly or indirectly to infection or to chemical agents. In their experience, clinical features of single cases are of little help in determining etiology, and tests of hepatic function have from the etiologic standpoint been largely fruitless. It is pointed out that syphilis is one of the infectious diseases that can cause hepatitis. It is stated that half the fatal cases of congenital syphilis show liver involvement, that some evidence of syphilis of the liver is found in approximately 1 per cent of secondary syphilis, and that about 10 per cent of the severer cases progress to acute yellow atrophy. Arsenic is said to belong to the group of drugs considered hepatotoxic, and the mechanism is considered to be one of idiosyncrasy, hypersusceptibility or allergic sensitivity. Since syphilis itself can damage the liver, and its most powerful antidote is hepatotoxic, the disease together with arsenotherapy could certainly be expected to produce liver damage from time to time. Ottenberg and Spiegel found reports in the literature quoting the incidence of so-called "arsenical jaundice in syphilotherapy" as approximately 1 per cent or less. Comparing these figures with those of Kulchar and Reynolds,⁶⁵ one would suspect that the prison inmates treated by the latter may have been strongly influenced by intercurrent infection of epidemic proportions. Ottenberg and Spiegel believe that bismuth is possibly a hepatotoxic drug, but that it is far weaker in that respect than is arsenic.

Kopp and Solomon⁶⁷ have studied the effect of prolonged trypanamide therapy on liver function. Their material consisted of 66 patients with syphilis of the central nervous system. In most cases the drug was given weekly in 3-gm. doses. One patient had received the amazing total of five hundred and thirty-nine injections of trypanamide. A number of them had also been treated with bismuth, trivalent arsenical therapy, or mercury or some form of fever therapy or both. Normal liver function was found in 16 of the patients. The remaining 50 revealed abnormal findings in one or more tests. Studies included the bromsulfalein test, phospholipids, fibrinogen, cholesterol esters, hippuric-acid excretion, icteric index, bilirubin, the van den Bergh reaction and the cephalin flocculation test. Abnormalities were slight enough to lead these authors to conclude that trypanamide causes relatively little liver damage even when given over a long period of time (as long as eighteen years) and combined with fever therapy. Jaundice occurring during therapy under all these circumstances is considered by Kopp and Solomon to cause no important damage to the liver and is not held to be a contraindication to the further use of trypanamide. It is sometimes surprising how much the human organism can tolerate.

Arsenical Reactions

Robinson⁶⁸ discusses reactions to arsphenamine from the standpoint of their effect on syphilis as well as on the patient. Severe exfoliative dermatitis and hepatitis have been thought at times to have a favorable influence on the course of the disease. Robinson reviews the cases of 381 patients who recovered from these complications and were followed for three months to twenty-one years. He found no evidence that severe treatment reactions of any sort play a part in the cure or amelioration of syphilis. He does not believe that arsenotherapy should be withheld from the patient who has seborrheic, atopic, contact or other itching dermatoses. This sounds a little dogmatic. It has been a matter of common observation that severe and extensive dermatoses may indeed be exacerbated by arsenotherapy and may progress to universal exfoliative dermatitis. Robinson outlines measures to avoid reactions of all types, the management of reactions and the factors to be considered before resumption of therapy, if it is to be resumed. He emphasized the well-known fact that exfoliative dermatitis is a positive contraindication to further arsenotherapy.

A method of circumventing reaction to arsenical drugs is described by Beerman, Pariser and Wammock.⁶⁹ The many reports in recent years regarding the possible value of vitamin C in the prevention of reactions led these investigators to study various solvents containing vitamin C for use as diluents in administering arsenic intravenously. Methylglucamine ascorbate was found to be the

most useful solvent. A 7 per cent solution of sucrose was utilized as the diluent. One hundred and fourteen patients who had exhibited some sort of reaction, usually mild, that on occasion necessitated the discontinuance of arsenical therapy were treated. This mixture seemed to have a beneficial effect on about half the patients who had had nausea and vomiting or nitritoid crises. One hundred milligrams of the ascorbic acid derivative was found to be the optimal dose.

Stephenson, Chambers and Anderson⁷⁰ report the annual statistics of the United States Navy on the toxic effects of arsenical compounds. One fatality from Mapharsen (from cerebral hemorrhage) is included in the current report. Total reactions from Mapharsen averaged one third as many as from neoarsphenamine. Dermatitis comprised 45 per cent of the total reactions, as compared with 55 per cent in the preceding year. The type of lesion was erythematous in 3 cases, exfoliative in 3 and macular, maculopapular, morbilliform and scarlatiniform in 1 each. Six cases of these dermatoses were mild, and 4 were severe.

Bismuth Eruptions

This subject is interesting, and it is doubted whether the average physician realizes either the frequency or the variety of dermatoses that can occur during bismuth therapy. Noojin and Callaway⁷¹ have reported on the subject of bismuth eruptions in antisymphilitic therapy. Acute eruptions are listed as erythematous, exfoliative, scarlatiniform, urticarial, purpuric and multiform and as similar to those of herpes zoster. Chronic bismuth eruptions may assume a pityriasis rosea type, lichen planus type, lichen simplex chronicus type (neurodermite), a fixed eruption or a generalized chronic eczematoid dermatitis. It should be emphasized that none of these are commonly observed. For that reason their occurrence may be confusing to those not treating large numbers of patients with syphilis.

SUMMARY

Although this year's report seems of considerable interest in its totality, a few items will bear re-emphasis.

Perhaps one of the most remarkable matters is the failure to follow up blood donors who have been found to have a positive serologic test for syphilis. It seems imperative that some means be found for all hospitals to do better with the problem. Other reports concerning the public-health aspect of syphilis control that are of considerable interest include good results in the operation of the Connecticut law governing premarital blood tests, the consultation program for local physicians provided by the State of New York, the so-called "facilitation process" employed in British Columbia to get at the source

of venereal disease and an encouraging reduction of the incidence of syphilis in the Army.

Syphilis in industry has received considerable mention in the recent literature. An outstanding example of the effectiveness of syphilis control in this field is the plan in use at the Remington Arms Company.

A most hopeful advance in the field of therapy is the use of penicillin for the treatment of syphilis. It is naturally too soon to go farther than to mention the possible successful treatment with this powerful drug. Considerable work is being continued in the field of intensive therapy, with various modifications in methods and encouraging results. The matter of increased reinfections following massive therapy is becoming of some importance.

The experimental use of arsenical drugs by intramuscular and oral administration in the treatment of syphilis seems hopeful. Should these procedures prove satisfactory, they would greatly enhance the ease of administration and the co-operation of patients.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30051

PRESENTATION OF CASE

An eighteen-year-old youth entered the hospital because of high blood pressure.

The patient was in excellent health until about seven months before admission, at which time he noticed the onset of occasional headaches. He had cold feet and legs at night, accompanied by hot flashes over the upper half of the body. Three months prior to entry he developed persistent nocturia, twice a night. There were one or two short episodes of dysuria, but no polyuria, pyuria, hematuria or incontinence. For years he had drunk two quarts of water daily. He had no increased thirst. About one month before admission he developed a sharp, occipital pain, which was accompanied by a dull ache over his eyes and over the bridge of his nose. At first the pain came on in the morning on waking, was relieved by work and returned in the afternoon or evening. Lately it had become persistent and prevented him from sleeping. About three weeks before admission, while being examined for a job, he was told that he had high blood pressure. The headaches became quite severe. Two days before admission he woke with a right facial paralysis. He had a slight nosebleed and palpitation, with slight nonradiating precordial pain, blurring of vision and mental confusion. He was unable to recognize his father. He had no vertigo, convulsion, unconsciousness, nausea, vomiting, fever, chills or anginal pains. He had lost 13 pounds of weight in two years.

The past history was entirely negative except for diphtheria as a child.

Physical examination showed a well-developed, well-nourished man in no distress. The lungs were clear. The left border of cardiac dullness was 8 cm. from the midsternal line in the fifth space. The sounds were forceful, regular, and of good quality. A loud third sound and a split second sound were heard at the base. The aortic second sound was greater than the pulmonic. There was complete right facial paralysis. No spasm, anesthesia or paresthesia was noted. The fundi showed rather marked generalized spasm. The disk margins were blurred, but there were no elevations; a few collections

*On leave of absence.

of cotton-wool exudate were seen, as well as two or three small bits of waxy exudate, in the left macula. Neurologic examination was otherwise negative except for bilaterally decreased tendon reflexes.

The blood pressure was 190 systolic, 140 diastolic. The temperature was 98.6°F., the pulse 80, and the respirations 20.

Examination of the blood showed a red-cell count of 5,700,000, with 14.5 gm. of hemoglobin. The white-cell count was 14,500, with 66 per cent neutrophils. The urine showed a specific gravity of 1.020. There were three or four red cells and one or two white cells in the sediment. The culture was negative. The stools were guaiac negative. A blood Hinton test was negative. The nonprotein nitrogen was 28 mg. per 100 cc.

X-ray examination of the chest showed slight enlargement of the left ventricle. An intravenous pyelogram was negative. A urine concentration test showed a specific gravity of 1.022. A phenol-sulfonephthalein test revealed 40 per cent excretion in the first fifteen minutes, and 85 per cent in two hours. A lumbar puncture gave an initial pressure of 120 mm. of water; 10 cc. of clear colorless fluid was withdrawn, with a final pressure of 80 mm. There were 3 white cells per cubic millimeter, with a total protein of 82 mg. per 100 cc. The gold-sol test was 0011331000. Repeated blood-pressure determinations gave an average of 200 systolic, 140 diastolic, while lying down and sitting, and one of 150 systolic, 130 diastolic, while standing. The entire determination, however, was done in a single sitting over a period of only twenty-four minutes. A cold pressor test showed a systolic rise of 10 mm. and a diastolic rise of 10 mm. Blood-pressure determination after the administration of three doses of 3 gr. of sodium amytal within a period of three hours showed no definite change. An electrocardiogram revealed a normal rate of 85. The PR interval was 0.12 second; S₂ and S₃ were prominent; ST₂ and ST₃ were depressed, with increased T₂ and T₃.

The patient's condition remained essentially the same. There was a slow rise of blood pressure. On the sixth hospital day he developed a sore throat, with chilly sensations and increased sweating. The temperature rose to 102°F. Examination showed a beefy-red throat and bilaterally tender and enlarged posterior cervical lymph nodes. The white-cell count was 13,800, with 78 per cent neutrophils. A throat culture showed many beta-hemolytic streptococci. On the sixteenth hospital day he was given 2 gm. of sulfadiazine every two hours for two doses, followed by 1 gm. every four hours for six days. The throat culture became negative.

On the twenty-first hospital day he complained of discomfort in the right flank. There was some tenderness in the right costovertebral angle. The urine examination showed a specific gravity of 1.010 and a + test for albumin. The urine contained innumerable red cells, with occasional white cells and

granular casts, which persisted for five days. A urine culture was negative. The temperature, pulse and respirations were normal. The blood pressure was 220 systolic, 165* diastolic. An operation was performed on the twenty-sixth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. HARRY A. DEROW*: We are dealing with an eighteen-year-old boy with severe progressive arterial hypertension and without any history of antecedent renal or hypertensive disease. The onset of this condition apparently dated from about seven months prior to admission to this hospital. Because of the high diastolic pressure and the retinal picture of papilledema, cotton-wool spots and diffuse arteriolar spasm, we have to make a diagnosis of malignant hypertension. By making this diagnosis we are not referring to any specific pathologic process in the kidneys: that is, the term "malignant hypertension" is used as a clinical diagnosis.

Back in 1935, Dr. Mark Altschule and I^{1,2} pointed out that malignant hypertension is a syndrome that may occur with no evidence of existing hypertension, as the end stage of primary (essential) hypertension or as the end stage of a miscellaneous group of conditions characterized by secondary hypertension. We also pointed out that during the life of the patient exhibiting the syndrome of malignant hypertension it is usually difficult if not impossible to determine the nature of the underlying pathologic process, that the prognosis by and large of these patients is extremely poor and that the cases that offer some modicum of hope are those rare surgically amenable cases in which the syndrome has been precipitated by renal infarction or by the development of certain tumors of the adrenal gland (pheochromocytomas). Also, there are cases of malignant hypertension that despite the poor prognosis, develop spontaneous remissions, during which the fundi show amazing improvement. The blood pressure, however, remains the same and these patients may go on for a period of years only to succumb to the same rapidly progressive picture that they originally presented.

In this patient, what evidence do we have to indicate antecedent primary inflammatory renal disease? I should like to ask about the urine examinations. The number of examinations done is not given; also the presence or absence of albumin is not stated.

DR. BENJAMIN CASTLEMAN: A + and a ++ test were recorded in three out of nine examinations.

DR. DEROW: The fact that six of the nine urine specimens that were examined failed to show albumin makes me believe that we are probably not dealing with primary inflammatory renal disease upon which malignant hypertension has been super-

imposed.³ I am unable to interpret the history of one or two short episodes of dysuria three months before entry, particularly since there was no pyuria, hematuria or incontinence. On the other hand, it is possible for patients with chronic inflammatory renal disease causing albuminuria to go along for many years without symptoms of any kind, with intact kidney function and with normal blood pressure, only to develop suddenly the picture that this patient presented. The normal intravenous pyelogram probably rules out polycystic kidneys or other congenital anomalies of the upper urinary tract. The possibility of an adrenal tumor cannot be eliminated by the finding of a normal pyelogram, and that of course is a possibility here. There is no mention made of scalloping of the ribs or of the blood-pressure values of the legs, so I think that we can probably eliminate coarctation of the aorta.

The possibility of a brain tumor is unlikely, because the patient presents the picture of scattered focal lesions in the cortex, midbrain, and pons, and it is difficult to visualize a brain tumor that would involve such dispersed areas. My explanation for the cerebral picture is that there were scattered necrotic vascular foci, which are often seen in patients with severe hypertension.

We are left with the diagnosis of the syndrome of malignant hypertension without any clear idea of the underlying renal lesion. There does not seem to be any impairment of renal or cardiac function, and the clinical picture is chiefly that of cerebral disease.

The clinical course of the patient is interesting. On the sixth day, he developed a streptococcal sore throat, and because of the persistence of a positive throat culture, he was given sulfadiazine. There is a question, of course, whether the throat culture would not have become negative in the course of time and whether sulfadiazine should have been given in the absence of active streptococcal infection. There is a difference of opinion on this matter. Not so long ago I had occasion to discuss with Dr. Maxwell Finland the matter of the administration of sulfadiazine to patients in the carrier state, and he is one who believes that sulfadiazine should not be given. The attending physicians probably wanted to eliminate the throat as a source of infection as quickly as possible prior to whatever operative procedure was going to be undertaken. During the course of the sulfadiazine therapy the patient developed discomfort in the right flank, tenderness in the right costovertebral angle, albuminuria, hematuria, pyuria and cylindruria. There is no mention made of the development of edema, nor of the urinary volume, during this period of what seems to be a renal complication following the administration of sulfadiazine. Is there any information in that regard?

DR. CASTLEMAN: No.

DR. DEROW: The note does appear, however, that the diastolic pressure was elevated above the levels that were previously recorded. From the history

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30051

PRESENTATION OF CASE

An eighteen-year-old youth entered the hospital because of high blood pressure.

The patient was in excellent health until about seven months before admission, at which time he noticed the onset of occasional headaches. He had cold feet and legs at night, accompanied by hot flashes over the upper half of the body. Three months prior to entry he developed persistent nocturia, twice a night. There were one or two short episodes of dysuria, but no polyuria, pyuria, hematuria or incontinence. For years he had drunk two quarts of water daily. He had no increased thirst. About one month before admission he developed a sharp, occipital pain, which was accompanied by a dull ache over his eyes and over the bridge of his nose. At first the pain came on in the morning on waking, was relieved by work and returned in the afternoon or evening. Lately it had become persistent and prevented him from sleeping. About three weeks before admission, while being examined for a job, he was told that he had high blood pressure. The headaches became quite severe. Two days before admission he woke with a right facial paralysis. He had a slight nosebleed and palpitation, with slight nonradiating precordial pain, blurring of vision and mental confusion. He was unable to recognize his father. He had no vertigo, convulsion, unconsciousness, nausea, vomiting, fever, chills or anginal pains. He had lost 13 pounds of weight in two years.

The past history was entirely negative except for diphtheria as a child.

Physical examination showed a well-developed, well-nourished man in no distress. The lungs were clear. The left border of cardiac dullness was 8 cm. from the midsternal line in the fifth space. The sounds were forceful, regular, and of good quality. A loud third sound and a split second sound were heard at the base. The aortic second sound was greater than the pulmonic. There was complete right facial paralysis. No spasm, anesthesia or paresthesia was noted. The fundi showed rather marked generalized spasm. The disk margins were blurred, but there were no elevations; a few collections

of cotton-wool exudate were seen, as well as two or three small bits of waxy exudate, in the left macula. Neurologic examination was otherwise negative except for bilaterally decreased tendon reflexes.

The blood pressure was 190 systolic, 140 diastolic. The temperature was 98.6°F., the pulse 80, and the respirations 20.

Examination of the blood showed a red-cell count of 5,700,000, with 14.5 gm. of hemoglobin. The white-cell count was 14,500, with 66 per cent neutrophils. The urine showed a specific gravity of 1.020. There were three or four red cells and one or two white cells in the sediment. The culture was negative. The stools were guaiac negative. A blood Hinton test was negative. The nonprotein nitrogen was 28 mg. per 100 cc.

X-ray examination of the chest showed slight enlargement of the left ventricle. An intravenous pyelogram was negative. A urine concentration test showed a specific gravity of 1.022. A phenol-sulfonephthalein test revealed 40 per cent excretion in the first fifteen minutes, and 85 per cent in two hours. A lumbar puncture gave an initial pressure of 120 mm. of water; 10 cc. of clear colorless fluid was withdrawn, with a final pressure of 80 mm. There were 3 white cells per cubic millimeter, with a total protein of 82 mg. per 100 cc. The gold-sol test was 0011331000. Repeated blood-pressure determinations gave an average of 200 systolic, 140 diastolic, while lying down and sitting, and one of 150 systolic, 130 diastolic, while standing. The entire determination, however, was done in a single sitting over a period of only twenty-four minutes. A cold pressor test showed a systolic rise of 10 mm. and a diastolic rise of 10 mm. Blood-pressure determination after the administration of three doses of 3 gr. of sodium amytal within a period of three hours showed no definite change. An electrocardiogram revealed a normal rate of 85. The PR interval was 0.12 second; S₂ and S₃ were prominent; ST₂ and ST₃ were depressed, with increased T₂ and T₃.

The patient's condition remained essentially the same. There was a slow rise of blood pressure. On the sixth hospital day he developed a sore throat, with chilly sensations and increased sweating. The temperature rose to 102°F. Examination showed a beefy-red throat and bilaterally tender and enlarged posterior cervical lymph nodes. The white-cell count was 13,800, with 78 per cent neutrophils. A throat culture showed many beta-hemolytic streptococci. On the sixteenth hospital day he was given 2 gm. of sulfadiazine every two hours for two doses, followed by 1 gm. every four hours for six days. The throat culture became negative.

On the twenty-first hospital day he complained of discomfort in the right flank. There was some tenderness in the right costovertebral angle. The urine examination showed a specific gravity of 1.01 and a + test for albumin. The urine contained innumerable red cells, with occasional white cells and

*On leave of absence.

nucleate from the adrenal gland. A renal biopsy was also performed.

Microscopically the tumor is a pheochromocytoma, — a tumor of the medulla, — but it is of an unusual type. The cells are arranged in a pattern somewhat reminiscent of a neuroblastoma (Fig. 1). I suppose it is possible to have a tumor containing both these types of cells, since originally they arose from the same sympathetic primitive cell or sympathogonia.

DR. DEROW: Did you find acute hemorrhage in the tumor to explain the development of the symptoms that the patient had?

DR. CASTLEMAN: No; just foci of necrosis that you may find in any actively growing tumor.

DR. R. H. SMITHWICK: What did the renal biopsy show?

DR. CASTLEMAN: A perfectly normal kidney, with no evidence of arteriolar disease.

This patient has been well and free from hypertension since his operation two years ago, and a sympathectomy was not necessary on the other side. The cause of his hypertension, therefore, although it was not of the paroxysmal type, was the adrenal tumor.

DR. REGINAID H. SMITHWICK: This case is one of the few with pheochromocytoma without paroxysmal hypertension. I think it is well to stress the fact that this is an extremely rare condition. The great majority of reported cases with pheochromocytoma have had definite paroxysmal hypertension. So far as I know there are only one or two cases in the literature that in any way compare with this one; hence, it is difficult to make a diagnosis of pheochromocytoma in the absence of paroxysmal hypertension.

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CASE 30052

PRESENTATION OF CASE

First admission. A sixteen-year-old schoolgirl was admitted because of high blood pressure.

The patient had pseudoarthrosis of the left leg at the age of three, and several operations were performed in various community hospitals. She had diphtheria, measles, chickenpox, whooping cough, tonsillitis and pneumonia as a child, but no history of kidney disease was known. Five months before entry she had an attack of dizziness, headache and unconsciousness, resulting in "complete left hemiplegia." Prior to that time the determination of her blood pressure was of questionable veracity, but one determination eighteen months previously was reported as "112." She was admitted to a community

hospital, where the blood pressure was found to be 180 systolic, 120 diastolic. There was a complete left hemiplegia, with slowing of the speech. The spinal fluid was grossly bloody. During the course of the next three weeks the fluid gradually cleared, and the patient began to have some return of function in the arm and leg. The blood-pressure readings varied between 240 systolic, 180 diastolic, and 180 systolic, 110 diastolic. She was found to have a urinary-tract infection and was put on "adequate dosage of sulfadiazine." A urine-concentration test performed at that time showed a fixed specific gravity of about 1.010. A phenolsulfonephthalein test showed 70 per cent excretion in two hours, with 20 per cent in the first twenty minutes. An insulin tolerance test was normal. The paralysis of the face and slurring of the speech disappeared, and there was some improvement in the left leg and arm. She was then transferred to this hospital.

Physical examination showed a well-nourished girl with many brown nevi scattered over the entire body. There was a dorsal scoliosis. The left leg was 7.5 cm. shorter than the right. Excessive hair was present over the arms, legs and abdomen. The heart and lungs were normal. There was deep tenderness in the left flank, and a feeling of fullness, but no masses. Neurologic examination showed papilledema, old and new retinal hemorrhages and albuminuric spots. She was unable to count fingers with either eye. There was a left hemiparesis, and spasticity of the left leg with hyperactive reflexes. The Hoffmann, Oppenheim, Chaddock and Babinski signs were positive on the left.

The blood pressure was 160 systolic, 120 diastolic. The temperature was 99°F., the pulse 80, and the respirations 20.

Examination of the blood showed a red-cell count of 4,610,000, with 13.8 gm. of hemoglobin. The white-cell count was 6500, with 68 per cent neutrophils. A blood Hinton test was negative. The urine was cloudy, with a pH of 5.5. The specific gravity was 1.018. Two to 4 white cells per high-power field were seen in the sediment. The stools were negative.

The blood nonprotein nitrogen was 20 mg. per 100 cc., the blood sugar 88 mg., and the cholesterol 186 mg. A urine-concentration test showed that the specific gravity was 1.022-1.028. There was no albumin. A phenolsulfonephthalein test was normal. The 17-ketosteroids were 8.4 mg. per 100 cc. in twenty-four hours. The test for follicle-stimulating hormone was positive for at least 6.5 mouse units per twenty-four hours. An electrocardiogram showed a normal rate of 80. The PR interval was 0.14 second. ST₁ was slightly depressed. In Lead 3, the ST segment was slightly elevated and the P and T waves were low.

An x-ray film of the chest showed a slightly enlarged heart. The left ventricle was more rounded than usual. The aorta was slightly tortuous but not dilated. The lungs were clear. An intravenous

pyelogram was negative. Numerous blood-pressure determinations gave averages of 188 systolic, 140 diastolic, while lying down, of 180 systolic, 145 diastolic, while sitting and of 192 systolic, 152 diastolic, while standing. A cold pressor test gave a blood pressure of 220 systolic, 170 diastolic.

She remained essentially the same, and on the twenty-second day a right lumbodorsal sympathectomy was performed. Postoperatively there was no striking change in the blood pressure. On the thirty-seventh day a left lumbodorsal sympathectomy was performed. The blood pressure was not affected, and she was asymptomatic until the sixth postoperative day, when she had a generalized convulsion lasting about five minutes, with associated urinary incontinence and biting of the lips. During the attack the head was turned to the right and there was considerable frothing at the mouth. Following the attack the blood pressure was 260 systolic, 170 diastolic.

Six days later she had "a second brief seizure." Four days later a lumbar puncture gave an initial pressure of 180 mm. of water, and 3 cc. of clear fluid was withdrawn. The total protein was 213 mg. per 100 cc., and there were no cells. The vomiting and headache persisted. The patient complained of inability to see. Examination of the fundi showed 4 to 5 diopters of choking of the right disk, and 3 of the left. X-ray examination of the skull was negative. A second lumbar puncture, eight days after the previous one and performed at the height of a headache, showed an initial pressure of 310 mm.; 10 cc. of clear colorless fluid was withdrawn. A subtemporal decompression was performed. The blood pressure was 240 systolic, 190 diastolic. The blood nonprotein nitrogen was 18 mg. per 100 cc. The patient eventually improved and was discharged on the eighty-sixth hospital day.

Final admission (five days later). The patient remained well until two days before admission, when she had seven convulsive seizures and became unresponsive.

Examination showed an emaciated, stuporous girl with a left hemiplegia and a positive Babinski on the right. The decompression site was bulging. The blood pressure was 255 systolic, 175 diastolic, the temperature 102°F., the pulse 120, and the respirations 20.

The urine was acid, with a specific gravity of 1.020 and positive tests for diacetic acid and acetone; the sediment contained 1 to 5 white cells and 1 to 5 red cells per high-power field. The nonprotein nitrogen was 45 mg. per 100 cc., the carbon dioxide combining power 23.3 millimols per liter, and the chloride 100.5 milliequiv. per liter.

The patient failed to regain consciousness and died on the fourth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. PAUL D. WHITE: The pseudoarthrosis, I suppose, represents a fracture.

Apparently there was a sudden fulminating onset to this illness.

The blood pressure was consistent with malignant hypertension.

"She was found to have a urinary-tract infection and was put on adequate dosage of sulfadiazine. Previously, she had had no history of kidney infection, and I wonder if this was not secondary to serious prolonged illness rather than an important primary factor.

The relation between the hemiplegia due to cerebral lesion, whatever it may have been, and blood pressure is of prime interest. I wonder which was cart and which was horse.

The hirsutism impressed me, and I looked for other manifestations along this line to indicate something like Cushing's disease, but that was not found. It may suggest adrenal hyperplasia.

The abdominal examination leaves me uncertain whether or not a tumor was present in the left flank.

The severe retinopathy might certainly have been hypertensive.

The difficulty with sight was much more marked than that usually seen in hypertensive retinopathy and suggests optic atrophy.

I was not sure what the Hoffmann sign was, and I looked it up. It is flexion of the terminal phalanx of the thumb and of the second and third phalanx of the fingers when the nails are suddenly pressed. The Oppenheim is extension of the toes when the inner side of the leg is scratched or stroked. Chaddock is positive when, on irritating the external malleolar skin area, the great toe extends, as in case of organic disease of the corticospinal reflex pathway it resembles the Babinski.

The laboratory findings were essentially negative. Dr. Albright told me this morning that a value of 8.4 mg. for the 17-ketosteroids is a normal finding. The electrocardiogram was normal. It looks as if aortic disease was not present, but that there may have been a little hypertensive heart disease, with increase in the size of the left ventricle.

After the first operation "there was no striking change in the blood pressure." One does not expect a drop that early even if the result is eventually successful. The blood pressure should have been affected by the second operation, however, if the procedure was going to be beneficial. All the cases that I have seen that were successful had an early drop in blood pressure after the second operation.

The episode on the sixth postoperative day sounds like an epileptic fit.

There apparently was no deformity of the vertebrae, and the bones were not porous. The temporal decompression was evidently done to relieve pressure.

We have three chief problems: first, the cause of the hypertension; second, the relation of the hypertension to the cerebral lesion; and third, the cause of death. I do not believe that there is any good

vidence for renal etiology, for coarctation of the aorta or for subarachnoid hemorrhage, either primary or secondary. Hypertension may be found in cases with subarachnoid hemorrhage, but usually the blood pressure is normal and is not elevated much by such a hemorrhage.

I have read over the features of Cushing's syndrome, — that is, basophilic adenoma of the pituitary, — and this case does not seem to fit. The girl was not painfully obese, nor did she have striking sex changes. Also, the hypertension seems much too great. I do not recall having cases with such a high pressure brought to my attention. The adrenocortical syndrome does not fit either, that is, with tumors in the usual sites, unless Dr. Smithwick, who did this operation, removed one that we may hear about later and unless something else came from it. I know that Dr. Smithwick in his lumbodorsal splanchnic resections explores the kidneys and the ordinary sites of adrenal tumors. Could there have been a simple cortical adrenal hyperplasia, unidentifiable by gross inspection, that produced the situation found in this patient?

A rare ovarian tumor, known as arrhenoblastoma, has been noted to cause hypertension and excessive hair, without hyperglycemia or osteoporosis. But there is no evidence of that here. There was a suggestion of something in the left flank, but I cannot diagnose such a tumor on that basis.

Essential hypertension is possible even at an early age, but it must be considered as extremely rare under twenty. Some, probably considerable, evidence against such a diagnosis is the failure of bilateral lumbodorsal splanchnic resection to budge the blood pressure. In every young person with essential hypertension that I have known who has been operated on by Dr. Smithwick there has been a distinct change in the blood pressure after bilateral lumbodorsal sympathectomy. I should like a comment on that from Dr. Smithwick himself.

Finally, one must consider a brain tumor that involved, by pressure, the temporal area and motor cortex on the right and the optic nerves, with initial hemorrhage into the ventricles and spinal canal and resulting secondarily in generalized hypertension.

DR. JOHN ABBOTT: May I contribute one item that is not recorded in the history? An electroencephalogram indicated a lesion of the motor cortex, maximal in the right temporal region.

DR. WHITE: I thought from the data I had that brain tumor might be the best bet, but it is extremely rare in my experience to be asked to see anyone with hypertension of which brain tumor is the cause. Of course cerebral hemorrhage can be induced by either hypertension or brain tumor. I should like to ask the neurologic experts how much vascular hypertension can be produced by a brain tumor. I think that it is much less likely to discover in such a young person what we might find in a middle-aged or older

person — namely, cerebral vascular disease with apoplexy secondary to essential hypertension.

If it was a tumor, I do not know the type. Perhaps it was a glioma. A metastatic tumor in the brain has to be considered. I was rather intrigued by the thought that it might have been a hypernephroma; but that is very, very rare.

CLINICAL DIAGNOSIS

Hypertension.

DR. WHITE'S DIAGNOSIS

Hypertension and cerebral hemorrhage of unknown cause, perhaps due to brain tumor.

ANATOMICAL DIAGNOSES

Occlusion of orifices of renal arteries: complete (right) and partial (left).

Arteriosclerosis: left kidney, spleen, pancreas and brain.

Cardiac hypertrophy, hypertensive type.

Cerebral infarction, with secondary hemorrhage: right lenticular nucleus.

Bronchopneumonia, terminal.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The striking finding was in the orifices of the renal arteries in the aorta. In place of the orifice of the right renal artery we were able to find only a dimpling of the intima; the proximal 6 mm. of the vessel was narrowed by fibrous tissue to a mere pinpoint, if open at all (Fig. 1). Then the vessel abruptly became patent, with a circumference of about 10 mm., the point of dilatation being where the suprarenal branch was given off. The orifice of the left renal artery, although not occluded by fibrous tissue like the right, was markedly constricted to about 1 mm. in diameter for a distance of about 3 mm.; it then dilated to about 15 mm. in circumference. Distal to the occlusion on the right and within the narrowed portion on the left were small, fairly recent thrombi. We have, therefore, a situation in man analogous to the Goldblatt dog; in which hypertension is produced by clamping both renal arteries. I am at a loss to explain the pathogenesis of this process. Microscopic examination of sections through the points of occlusion and narrowing show merely old organized fibrous tissue, which may at one time have been thrombi superimposed on an arteriosclerotic lesion.

Another interesting finding was the presence of a moderate degree of arteriolar sclerosis in the left kidney and none in the right. This is also somewhat analogous to the rare form of hypertension due to a unilateral ischemic kidney, in which arteriolar changes are found only in the opposite kidney.

The heart was enlarged, weighing 300 gm.

The changes in the brain were those of an infarct with secondary hemorrhage, at least that is what Dr. Kubik believes it to be rather than the result of cerebral hemorrhage. There was severe diffuse vascular disease in the small vessels of the brain.

DR. REGINALD H. SMITHWICK: We now have several hundred cases of hypertension treated surgically, and Dr. Castleman has dipped into this

adrenal glands. As you can see, this case here about as close a counterpart of the Goldblatt syndrome in dogs as one could possibly see in a human being, and as I have said, is the only case in our experience. The only thing that was missing was actual presence of the clamp itself.

DR. WHITE: What did you think after the operation failed to bring down the pressure? You thought that something was wrong?

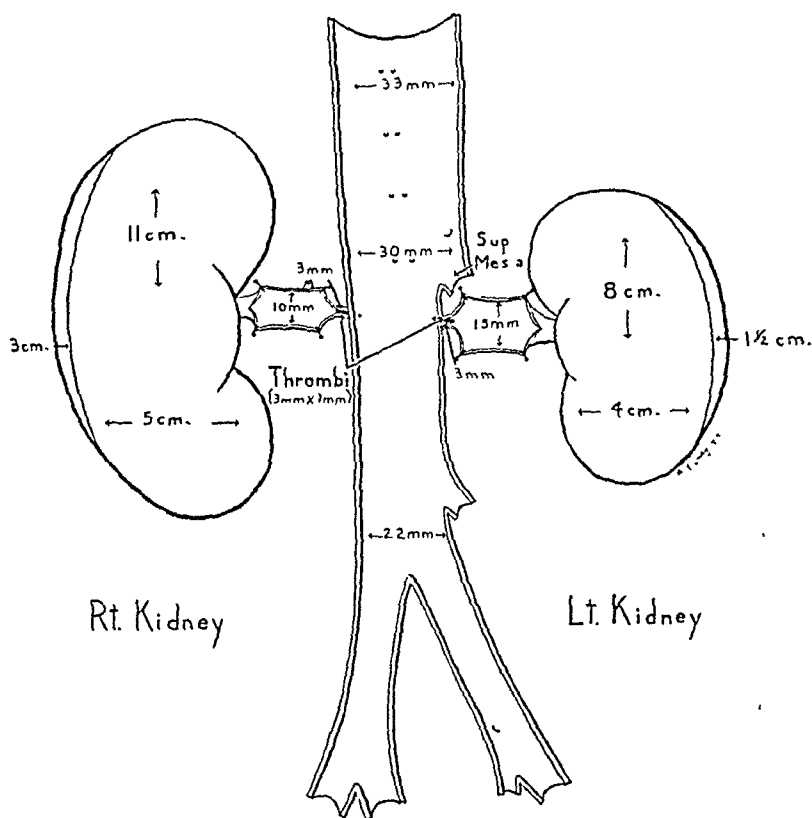


FIGURE 1. Schematic Drawing of Arterial Supply of Kidneys Showing Occlusion of the Orifices of the Renal Arteries.

group and selected two of the rarest for discussion today. The second case is the only example of this sort in the series, and I have never come across such a case in the literature.

DR. WHITE: Did you find this at operation?

DR. SMITHWICK: No, because the occlusions were practically within the aorta. The operative field permits careful examination of most of the renal artery, the kidney and the adrenal gland; the extra-aortic part of the renal artery, however, did not impress me as being particularly remarkable. Incidentally, it is extremely important, in any operation for hypertension, to include exploration of the kidneys and

DR. SMITHWICK: Yes, because that was no I anticipated.

DR. WHITE: What percentage do you bring at that age?

DR. SMITHWICK: Between 80 and 90 per cent.

DR. WHITE: Dr. Ayer, how often do you see hypertension with brain tumor?

DR. JAMES B. AYER: We rarely see as much tension as this patient showed.

DR. WHITE: The association of hypertension and brain tumor is commonly referred to in text but I wonder how often you actually encounter

DR. AYER: Practically never.

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PATULIN AND THE COMMON COLD

"WHAT'S good for a cold?" This question has always been certain to embarrass physicians since they, too, would be glad to have the answer to that question and employ it whenever they were troubled by this common malady. When a remedy for the common cold is offered, and particularly if that remedy happens to be in the form of an agent related to such a widely hailed and effective substance as penicillin, it is easy to understand why physicians and the lay public are both interested and intrigued. Such a remedy is discussed in a recent issue of the *Lancet*,* which contains a report on the use of patulin

in the common cold. This study is the result of a collaborative research by a group of biochemists in the London School of Tropical Medicine and Hygiene and by a number of clinical investigators.

Patulin is the name given to a substance obtained as a metabolic product from the filtrate of cultures of *Penicillium patulum*. This new agent is of great interest for several reasons. The active substance has been isolated and crystallized, and its chemical structure has been defined. It happens to be a relatively simple chemical compound. The yields of this material from cultures are relatively large as compared with those of similar products, such as penicillin. Furthermore, it seems to be equally effective against both gram-positive and gram-negative bacteria. Against the gram-positive organisms it is less effective than penicillin, whereas against the gram-negative ones it is more effective. The substance is quite stable in the crystalline form, but some changes do take place if an aqueous solution is permitted to stand at room temperature for several days. It is not inactivated by either serum or pus.

On the other hand, the results of toxicity experiments indicate that this drug has a much narrower range of safety between concentrations that are effective and those that are toxic. In acute toxicity experiments the average lethal dose was 0.5 mg. for a 20-gm. mouse. This amount given either intravenously or subcutaneously produced death accompanied by widespread capillary damage in the liver, spleen and kidneys as well as pulmonary hemorrhages and edema. Convulsions occurred soon after the material was given intravenously. Similar toxicity was observed in rabbits with even smaller amounts. When injected subcutaneously in animals, it produced local necrosis. The substance was also toxic to leukocytes. It was found that phagocytosis of killed staphylococci by leukocytes was unaffected by a dilution of 1:8000 but was completely inhibited when a dilution of 1:2000 was used.

The reported clinical trials concern only its use in the common cold, which is usually considered to be a virus disease. Cases having a protracted course are usually those in which the virus infection is followed by a bacterial complication of the nose,

*Rastriek, H., and others. Patulin in common cold. Collaborative research on derivative of *Penicillium patulum* Bainier. *Lancet* 2:625-635, 1945.

pharynx or accessory nasal sinuses. Such complications are the result of infection with the common respiratory pathogens, and these appear to be amenable to the use of patulin. The method used in the clinical trials consisted of either spraying the nose and throat, douching the nose, or sniffing. It was used in a buffered aqueous solution and administered every four hours in dilutions of 1:5000 to 1:20,000. The more concentrated solution produced local irritation, some patients complaining of transitory stinging and others of a profuse nasal discharge for about half an hour. This was not noted with the more dilute solutions. Apparently no other ill effects were observed.

Interestingly enough, the first clinical trial was by Dr. W. E. Gye, director of the Imperial Cancer Research Fund Laboratory, who was given a supply of the material for an experimental study of its effect in cancer. Dr. Gye was suffering from a severe cold at the time that he received the substance so he made up a solution, sniffed it and was rapidly relieved of his symptoms. He then supplied some of the material to colleagues, who likewise felt that the chief symptoms of their colds were rapidly alleviated. Dr. Gye's note makes no mention of the effect of this substance in experimental cancer.

The material was then supplied to Surgeon Commander Hopkins, of the Royal Navy, who reported on the antibacterial efficacy of the drug as well as on its toxicity in animals. He also set up two types of clinical study: a control series among officers and enlisted men who volunteered for treatment and an evaluation of the clinical effects based on careful notes by colleagues and friends. The cases were carefully selected to exclude persons who already had evidence of complicating infections and also to eliminate cases of clinical influenza. The results of the control study showed that 58 per cent of 95 persons receiving patulin in various concentrations during the first few days of an uncomplicated cold were "cured" within forty-eight hours. In 85 control patients who received a solution of the buffer without patulin less than 10 per cent were benefited within this same period. The data were reviewed by Major Greenwood, a professor of epidemiology and vital statistics, and were found to be statistically significant. They calculated that the probability of

these results being a matter of chance was only three in ten thousand. A smaller number of cases diagnosed clinically as influenza were treated with beneficial effects. Interestingly enough, in those patients treated for the common cold who previously had had frequent colds that were followed by sinusitis, only temporary improvement was noted and sinusitis was not prevented when patulin was used presumably because the drug did not reach the infected areas.

Most of the physicians who were asked to use the material personally and to make careful notes of the results were quite enthusiastic. They stated that their symptoms were rapidly alleviated. On the other hand, this group also contained a number in whom symptoms of sinusitis were not prevented. In many of the subjects who responded favorably the acute symptoms often completely disappeared within a few hours; many, however, had a recurrence of discharge from and stuffiness of the nasal passages after a few hours and this was repeated several times before they were completely relieved. No effects were noted beyond the local irritation when the larger doses were used.

In view of the fact that the most serious types of complication of the common cold were not prevented, further elucidation of the mechanism whereby the results were obtained seems necessary. Although extensive clinical trials are indicated there is little prospect of any large supply being immediately available. Furthermore, a great deal more should be known about the pharmacological actions of the drug in human cases as well as in animals before any widespread use is permitted.

The fact that the chemical formula of the substance is known opens a wide field for further study. First of all, one may anticipate that it will be possible to synthesize this material. When sufficient materials are thus made available, one may anticipate numerous modifications of the chemical structure in the hope of reducing its toxicity and increasing its effectiveness, as has been true of the sulfonamides. In addition, the findings seem to justify extensive research on antibacterial substances from molds and other higher bacteria. One may expect much progress in this field in the next few years.

HOLMES AS A PSYCHIATRIST

The medical aspects of Holmes's career are being re-examined and re-evaluated. His place in American literature is secure, but many are asking what about his niche in American medicine? Did he, except for his outstanding contribution in 1843 to preventive medicine, the paper "On the Contagiousness of Puerperal Fever," exert any considerable influence on the trend of medical thought or leave buried in his writings material not fully appreciated at the time of its writing, or since? Undoubtedly the stamp of Holmes's dynamic character left an impression on a generation or more of the medical students who attended his anatomical lectures. He gave an impetus, moreover, to the public demonstration of the administration of ether by coining the term "anesthesia," stimulated research with the aid of the microscope and used his vast influence in 1875 to re-establish the Boston Medical Library for his generation and for posterity. These are, however, as time has listed them, minor contributions. What else did Holmes add to the medical scene? What about the "medicated novels," and Holmes as a psychiatrist?

Little attention has been paid to Holmes's interests in mental aberration or to Holmes as a clinical psychiatrist. It is now realized, thanks to the researches of Oberndorf,* that Holmes was long a profound student of mental disease and that he had pronounced and advanced ideas on mental mechanisms. • Possibly hesitant about presenting his thoughts before his medical colleagues, or at least doubtful about their acceptance in the form of a medical paper, he chose the medium of the novel to bring his opinions before the public. Neither *Elsie Venner* (1859) nor *The Guardian Angel* (1867) was a literary product of excellent quality when compared with contemporary works of Poe, Thackeray and Hawthorne. But they were studies of the abnormal mind, and simple though the stories are, both books give us an insight into Holmes's profound psychiatric understanding. His doctors, moreover, combine, as noted by Oberndorf, "those qualities so desirable in every physician but indispensable in a psychiatrist — namely, patience, forbearance,

tolerance, equanimity, accurate observation of the patient's actions and utterances, and unremitting consideration for the patient's psychological and environmental handicaps."

Following the novels, Holmes became so engrossed in the theme of the social significance of mental deviation that he chose this subject for his address to the Phi Beta Kappa Society at Harvard in 1871. "Mechanism in Thought and Morals," as the paper was called, was withheld from publication for more than twenty years, and only after careful revision, expansion and annotation had taken place, did Holmes allow it to appear in print, hidden in *Pages from an Old Volume of Life* (1892). There, this address, with its modern flavor and psychoanalytical leanings, has been allowed to rest nearly unnoticed. In this essay will be found opinions strangely similar to those so reluctantly accepted by the medical profession after they were re-emphasized by Freud forty years later. In the brain, Holmes considered, there persists a material record of thought; and secondly, this transmissible record is not at all times available to the person for the control of his actions. Are these ideas not the "indestructibility of infantile thought and impressions" and the "importance and influence of unconscious mentation" — the foundation stones of Freud's psychoanalytic structure? At least Oberndorf thinks so, and his book makes a strong case in Holmes's favor. Except for a pleasant whimsicality, so characteristic of Holmes, the following passage from his address might well have been written by Freud in 1910:

There are thoughts that never emerge into consciousness, which yet make their influence felt among the perceptible mental currents, just as the unseen planets sway the movements of those which are watched and mapped by the astronomer. Old prejudices, that are ashamed to confess themselves, nudge our talking thought to utter their magisterial veto. In hours of languor, as Mr. Lecky has remarked, the beliefs and fancies of obsolete conditions are apt to take advantage of us. We know very little of the contents of our minds until some sudden jar brings out the old stockings full of gold, and all the hoards that have hid away in holes and crannies.

MEDICAL EPONYM

SCHEUERMANN'S DISEASE

Dr. Holger Werfel Scheuermann (b. 1877), of Copenhagen, Denmark, described "Kyfosis dorsalis juvenilis [Juvenile dorsal kyphosis]" in the *Ugeskrift*

*Oberndorf, C. P. *The Psychiatric Novels of Oliver Wendell Holmes*. New York: Columbia University Press, 1943.

pharynx or accessory nasal sinuses. Such complications are the result of infection with the common respiratory pathogens, and these appear to be amenable to the use of patulin. The method used in the clinical trials consisted of either spraying the nose and throat, douching the nose, or sniffing. It was used in a buffered aqueous solution and administered every four hours in dilutions of 1:5000 to 1:20,000. The more concentrated solution produced local irritation, some patients complaining of transitory stinging and others of a profuse nasal discharge for about half an hour. This was not noted with the more dilute solutions. Apparently no other ill effects were observed.

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for laeger (82: 385-393, 1920). A German summary may be found in *Zeitschrift für Orthopädie und ihre Grenzgebiete* (41:305, 1921), and an English summary appears in *Acta Chirurgica Scandinavica* (54: 29, 1922). A portion of the latter follows:

Among spinal deviations at the age of puberty there are many cases which clinically and morphologically form a complete group. These are real fixed kyphoses in columna dorsalis or dorsolumbalis in arcuate form. . . .

The cause . . . lies, in my opinion, in the morbid condition of the growing-area between the epiphysis and corpus. . . .

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

EGAN — John J. Egan, M.D., of Gloucester, died January 22. He was in his seventy-fourth year.

Dr. Egan received his degree from Harvard Medical School in 1894. He was a member of the Massachusetts Medical Society and the American Medical Association.

Three sons and a daughter survive.

LOWENTHAL — Karl Lowenthal, M.D., of Fall River, died January 16. He was in his fifty-second year.

Dr. Lowenthal received his degree from Albert-Ludwigs-Universität Medizinische Fakultät, Freiburg, Baden, in 1915. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow survives.

STEIN — Albert Stein, M.D., of Thompsonville, Connecticut, died December 5, 1942. He was in his fiftieth year.

Dr. Stein received his degree from the University of Maryland School of Medicine and College of Physicians and Surgeons in 1917. He was a member of the Massachusetts Medical Society and the American Medical Association.

WAR ACTIVITIES

INDUSTRIAL MEDICINE

ALLOWABLE CONCENTRATIONS OF TOXIC DUSTS AND GASES

At a recent meeting of the committee of the American Standards Association concerned with approval of allowable concentrations of toxic dusts and gases, it was reported that six standards had been approved during the present calendar year, and that altogether twelve standards had been promulgated under the auspices of the committee since its reorganization two years ago.

The standards now being considered are on methanol, styrene monomer, formaldehyde, trichlorethylene and acrylonitrile. A standard on toluene has been approved and published. The proposed standards for oxides of nitrogen approved by the committee are now being processed through the Safety Code Correlating Committee.

Considerable discussion was given to the preparation of a standard for exposure to silica dust. It was finally decided to prepare a standard that would take into consideration the data now available for threshold limits for various industrial dusts with a silica content. The consensus was that no single maximum allowable concentration could be developed in view of the fact that no two dusts containing silica have the same effect on health, even when the silica content is the same.

The chairman was authorized to appoint subcommittees to consider the following standards: methyl chloride, which is now being used in place of Freon as a refrigerant; hydrofluoric acid, fluorine and fluorides; and radon, gamma rays and radium dust.

It was agreed by the committee that the recently circularized code on carbon tetrachloride should be rewritten, with a footnote to the effect that subjective symptoms may

be experienced when workers are exposed to concentrations lower than 100 parts per million and, for that reason, that attempts should be made to achieve concentrations lower than the standard recommended.

MISCELLANY

AMERICAN COLLEGE OF SURGEONS

Twenty-two cities throughout the United States and Canada have been selected by the American College of Surgeons as headquarters for one-day "war sessions" to be held in March and April. Advancements in military medicine and developments in civilian medical research and practice under the spur of the war emergency will be presented by authorities representing governmental agencies and by civilian physicians and surgeons. The meetings will be open to the profession at large, including medical officers of the Army and the Navy, residents, interns, medical students and executive personnel in hospitals. For the last, special hospital conferences, to be held simultaneously with the scientific sessions, are being arranged.

Each meeting will open at 8:30 a.m. with the showing of official Army and Navy films on medical and surgical subjects, such as evacuation of the wounded, fractures, bomb blast, burns and treatment of wounds. From 9:30 to 11:30, Army and Navy representatives who have been on active duty abroad will report; from 11:30 to noon, representatives of the United States Public Health Service will report on measures for the control of endemic and epidemic diseases. Current problems of the Procurement and Assignment Service will be presented by a representative at the luncheon conference from 12:15 to 2:00 o'clock. Between 2:15 and 5:00 scientific presentations by medical members of the armed forces and of the Veterans Administration and by civilian members of the medical profession, including someone engaged in the practice of industrial medicine, will be made. From 5:00 to 5:30 the need for protective service in time of war will be presented by a representative of the Office of Civilian Defense. The concluding session will be a dinner meeting and open forum with all participants in the day's program as the panel of experts to lead discussion of any and all subjects presented during the day, together with other problems of interest to the medical and hospital professions. The motion-picture showing, Public Health Service session, luncheon conference, Civilian Defense program and dinner meeting will be attended by both the medical and hospital groups. The hospital representatives will discuss wartime hospital problems and how they are being solved from 9:30 to 11:30, and will hold a round-table conference on "Wartime Hospital Service" from 2:15 to 5:00.

The preliminary schedule for the meetings is as follows:

DATE	CITY	STATES AND PROVINCES
February 28	Winnipeg	Manitoba, Saskatchewan
March 2	Minneapolis	Minnesota, North Dakota, South Dakota
March 4	Des Moines	Iowa, Nebraska, Missouri
March 6	Chicago	Illinois, Wisconsin
March 8	Cincinnati	Ohio, Kentucky, Indiana, West Virginia
March 10	Detroit	Michigan
March 13	Rochester	New York State
March 15	Toronto	Ontario
March 17	Montreal	Quebec, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland
March 20	Springfield	Massachusetts, Maine, New Hampshire, Vermont, Rhode Island, Connecticut
March 22	Philadelphia	Pennsylvania, New Jersey, Delaware
March 24	Baltimore	Maryland, District of Columbia, Virginia
March 27	Jacksonville	Florida, Georgia, North Carolina
March 29	Jackson	Eastern Tennessee, Mississippi, Louisiana, Western Tennessee, Alabama
April 1	San Antonio	Texas, New Mexico, Mexico
April 4	Tulsa	Oklahoma, Kansas, Arkansas
April 7	Denver	Colorado, Wyoming, Western Nebraska
April 11	Salt Lake City	Utah, Idaho
April 14	Spokane	Washington, Northern Idaho
April 18	Vancouver	Oregon, Montana
April 24	San Francisco	British Columbia, Alberta
April 27	Los Angeles	Northern California, Nevada, Southern California, Arizona

(Books Received on page ix)

ied the professional donors but also could call donors at any time when the supply of blood a particular group was too low. Soon this side of e business increased because one third of the trans- sions were among the private or semiprivate pa- ents. Because of available voluntary donors, the tire fund was never used; recently, because of a ortage of professional donors owing to the de- ands of war work, it has also grown so that there now about \$5000 on hand. This fund is most use- l for patients who require fresh blood; they send their voluntary donors at any time, and a pro- sional donor is sent for at the time the trans- sions are requested, fresh blood being furnished no extra charge. To keep up the supply of Rh- oods, these are purchased from the donor list or e Blood Grouping Laboratory (Children's Hos- tal, Boston). Before holidays or at any time when tra bloods of a given group are needed, pro- sional donors are sent for and a supply is laid in.

SYSTEM OF CREDITS AND DEBITS

Most fundamental to adequate service in a blood ink is a constant stream of donors well in excess of eds. Many banks have run into serious difficulties cause of neglecting this simple truth. For each hos- tal the problem is different. Prior to the establish- ent of our bank, we had plenty of available volun- ry donors, so that no shortage was anticipated beginning operation.

SYSTEM OF PATIENTS' CREDITS

To keep up a larger volume of deposits than of thdrawals, it was requested that for each trans- sion two or three bloods be deposited in the bank. urthermore, no blood is allowed to be issued to a itient who has no deposits on hand unless there is guarantee of cash replacement. To enforce this, the patient has no credit, permission for trans- sion must be obtained from one of the hospital rctors. The directors are moderately severe in rforcing this provision, with the result that neither e hospital staff nor the patients do much side- epping of obligations. The necessity for this is vious. In the first place, the patients' families rely replace bloods already received; in the second ace, it is difficult for a blood-bank nurse to refuse issue blood to a physician, whereas a director can adily do so if he thinks that little or no effort has en made to obtain donors. In worthy cases where ere is no credit, the director's permission is given r his signature on the requisition. This permission given freely, and by telephone in emergencies. To ep track of the patient's credit, a card file is main- ined in the bank, listing for each patient the num- r of donations of usable blood and the number of thdrawals for actual use. Blood withdrawn from e bank but not given, as happens occasionally, is a rule, charged to the patient, although in certain

cases the bank has accepted the loss. On the wards, the intern staff follows the patient's debit and credit on a deposit and withdrawal form marked with a rubber stamp. All this is complicated, but it actually saves both labor and disputes and provides a wise safeguard against profligate withdrawals.

Bloods do not expire with the passage of time on a patient's credit slip unless the patient leaves the hospital for a month or so. This is only fair, since blood costs the patient money and takes time and trouble to obtain. The blood bank loses nothing by permitting this or by relaxing its policy of maintain- ing credit beyond a month of absence in isolated cases. As a rule, the volume of blood coming in amply covers withdrawals, regardless of when the initial deposits were made.

SERVICE CREDIT

The record of credit or debit of the different serv- ices or divisions of the hospital is to the blood bank what a balance sheet is to commercial banks with this fundamental difference: Good service can be pro- vided only if there are ample amounts of four forms of currency, — that is, the four blood groups, — *whereas commercial banks deal with only one form.* Furthermore, two of the groups, Types B and AB, are rare. To be sure, to have enough blood on hand to care for a bleeding peptic ulcer in a Type AB patient a minimum of sixty bloods of all types must be on hand; in actual practice a minimum of eighty to one hundred is generally safer. Although there is no hesitation in using a carefully cross-matched universal donor's blood from a repeatedly typed professional donor in an emergency, or in switching to the original type after a fresh blood has been taken from a patient for cross-matching, it is still pre- ferred to administer a blood of the same group as the recipient's and an effort is therefore made to keep bloods as close to the one-hundred mark as possible.

In keeping to this standard, which is often difficult, the system of service credit is regarded as the most important factor. Under this system, the actual number of usable deposits made to the credit of a service — that is, by the donors for pa- tients on a service — is recorded on a blackboard, and from this are subtracted the bloods used by that service or belonging to it and expiring unused at the end of seven days. No credit is given for a blood of small quantity or with a positive serologic test or one that is considered otherwise unusable. This credit is much more real than the patient credit, for it represents actual blood on hand, less, of course, blood given out to the patients paying cash and for whom professional donors have not yet been purchased. Thus, when a blood is deposited for one of the surgical services but is actually given to a private patient who pays for it, it is listed to the credit of the surgical service long after it has ac- tually been used; at the same time the debit for this

blood is listed in the debit column under "professional donors." On each occasion when professional donors are sent for, the bloods used are subtracted from the debit column, the service not losing credit until a blood is actually given to its patient. This system is obviously open to criticism on the ground that the service credits of all services minus the debit for professional donors not yet sent for could readily equal zero and there would be no blood in the bank. To prevent this from occurring, a careful check is kept of bloods of all groups actually in the bank with an eye to preventing depletion. The number of bloods has on occasion gone as low as eight and as high as one hundred and thirty, but as a rule an average of sixty bloods is maintained, which cares for sixteen transfusions a day.

The enforcement of this system is, however, no less important than is the understanding of its functions. A credit is insisted on at all times. Although the issuance of bloods to a patient with credit is continued when the service has none, — and out of all fairness to patients, there could be no other course, — the responsibility for the debit is placed on the head intern or resident of the service involved. He is warned by the nurse in charge of the bank when his credit is low. How low it is depends on the volume of blood used, for the general surgical services, a low level is considered to be 6000 cc., because sick patients may exhaust this supply in a few days, whereas for the Dermatological Service a credit above 1000 cc. is considered high. A debit calls for admonition from the bank director to the resident. A lack of response is usually followed by an appeal to the chief of service by the bank director, and as a last resort, the director of the hospital is informed of the situation. It is rare that any person above the house staff has to be appealed to. This is only true because the co-operation of the chiefs of service and the support of the hospital director can be relied on. This system will only work in well-co-ordinated private hospitals.

When patients are transferred from one service to another, their credit goes with them. This works a hardship on the medical services but is on the whole fair, because the preoperative use of blood is equalled or exceeded by its operative or postoperative use; if credits remained stationary, the surgical services would often be unfairly in debt. Expiration of blood, causing a debit, is a great hardship; unfortunately, the only method of compensating for it is to maintain a great excess of donors over transfusions (high service credit). The benefit of expiration is that it means plenty of plasma for therapeutic or research purposes.

CARE OF DONORS

It is the responsibility of the doctor in charge of a patient to send for donors well in advance of the time needed. This responsibility sometimes de-

volves on a nurse at the Information Desk. This means that the patient's relatives frequently receive a slip of paper telling of banking hours and the rules about diseases and the taking of alcohol and food. If they are infrequent visitors to the hospital, they receive a telephone call, telegram or letter. The bank is open five afternoons a week, two evenings until 7 p.m., and on Saturday mornings. Tuesday afternoon is the only time for receiving donors by appointment, the reason being that many speak too little English and that others come from too long distances to keep exact dates. An attempt is made to receive donors for private patients or volunteer donors on Tuesday afternoons. Evenings are popular for war workers. Saturday afternoon and Sunday would be popular times for donors, but since attendance of the entire bank staff would be required they are avoided.

An effort is made to have donors looked after as far as possible by a volunteer worker, who makes out their cards, supervises their signing a release (these are needed in most states), and provides them with magazines and so forth while they are waiting. A history regarding contagious, debilitating and allergic diseases is taken, also the hour of last eating, alcohol ingestion, and the time of the last donation of blood. The history-taking and a brief physical examination, including the heart, the respiratory system, the blood pressure, the lymph nodes and, for males, the genitalia, are done by an intern. A blood smear is made and the hemoglobin and the temperature are determined by a technician. Donors are rejected if they have had transmissible, recent or debilitating diseases, are allergic, have eaten within the last four hours, or have taken alcohol within the last twelve hours. Abnormal blood smears and positive serologic reactions are cause for the discarding of blood. The main objection to recent eating lies in the elements of the donor's diet to which the patient is sensitive. This is also true of certain alcoholic beverages, but on the whole the main objection to the donor who has been drinking is lack of co-operation and frequent vasomotor collapse after phlebotomy. Donors of eighteen to seventy years of age are accepted outright, those under twenty-one years only with the permission of their families, and those over fifty-five only if in excellent condition, particularly so far as cardiac and peripheral vascular systems are concerned. Women weighing less than 100 pounds are usually rejected. On request of their physicians, patients with polycythemia, hypertension or decompensation are accepted as donors, but the blood of those with polycythemia is usually discarded, since it is too viscous to run freely. In a year's operation, between 16 and 20 per cent of donors were rejected on the ground that the giving of blood would be harmful to them or, more often, that their blood would be of poor quality or harmful to the patients.

When a donor is ready for phlebotomy, the outer clothing is removed and a clean gown and mask are put on. The donor is led into the bleeding room, where curtains are drawn between the tables so that he sees no blood being drawn. We do not agree with certain other bleeding centers that the observation of others being bled exerts no psychological effect or that, if it does, the effect is a beneficial one. We believe that the contrary is true, and our rate of syncope during phlebotomy is almost negligible. After termination of the procedure, the donor lies for five to ten minutes on the table, which is cushioned and soft; he is then escorted to a bed on low shock blocks in the recovery section, where milk,

tubing, which are washed with a high-speed water jet and soaked in N/10 sodium hydroxide, followed by thorough rinsing. The nurses who use the needles sharpen them on an electric grindstone, an important point in all intravenous work. The system of blood collection is a closed one operating by gravity instead of a vacuum — that is, there is an outlet on the head of the flask to permit the exit of air. A cotton air filter is inserted in the outlet to prevent contamination of the set by the entrance of air as the bottle cools after sterilization, or as air goes in and out with changes of room temperature and atmosphere pressure. These sets work well and are simple to operate. If the blood flow is slow, an

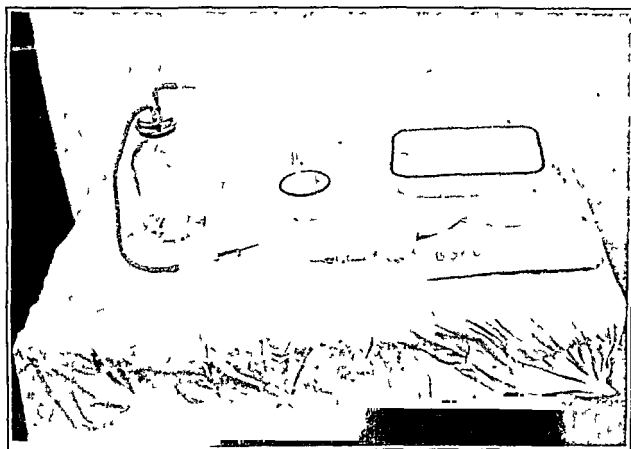


FIGURE 1. *The Blood-Withdrawing Set with Filter in Place.*

peanut butter and crackers are given. After a minimum of twenty minutes' rest, or longer if there is any feeling of faintness, the donor dresses and leaves the hospital. There have been rare cases of collapse after leaving the bank, but almost without exception these have occurred among donors who failed to follow the rules. Donors are sent cards giving their blood group and the date of donation, with room for more dates to be added.

THE TAKING OF BLOOD

The bleeding of a donor is regarded as an operating-room procedure and is carried out with complete sterile technic throughout. Under this system, the number of contaminated plasmas has been extremely low, so that it seems to be justified. The entire recipient set is autoclaved in heavy wrappings and is generally used within forty-eight hours of preparation. Great care is taken to clean all apparatus immediately after use, particularly needles and

Abbott suction bulb may be attached to the filter. Sixty centimeters of a 4 per cent solution of sodium citrate is used as an anticoagulant. The unnecessarily large amount is advantageous in preventing clots toward the end of the procedure or if more than 500 cc. of blood has inadvertently been drawn. This procedure has not increased hemolysis. Bacteriologic culture medium is inserted in the sets from time to time to check the effectiveness of sterilization.

The nurse taking the blood wears operating-room clothes and is gowned, scrubbed and gloved. The donor's arm is prepared for her by a nonsterile assistant with ether and then iodine. The needle (a No. 14 steel cannula with a glass adapter) is inserted through a novocain wheal without incision. The adapter gives prompt visual evidence of venipuncture. Only two tries are made on a donor, one on each arm, unless he is insistent on further ones. At the termination of the procedure, the tubing is clamped immediately above the flask on both the intake and outlet and cut. Blood for a Wassermann

test, blood grouping or determining the Rh factor is collected in two test tubes. The blood in the flask is agitated throughout the procedure and for half a minute afterward, since the anticoagulant is extremely diluted at the end, requiring extra shaking. The blood is allowed to cool to room temperature for half an hour before refrigerating, since slow cooling lessens hemolysis. The flask and its test tubes are labeled with the donor's number before they leave his side.

BLOOD STORAGE

Prior to the Wassermann report and the completion of grouping, bloods are stored by number in the

for type by letter, by color and by compartment; so also are the donors' cards. The bank book record acts as a check.

The temperature of the refrigerators and bottle coolers is kept at about 39°F. by means of thermostatic control. Prevention of a wide variation in temperature is carried out through the medium of thermometer dials on the outside of the boxes and an electric alarm system connected to the Maintenance Department, where there is someone on duty night and day. The compressors are set apart from the refrigerators to prevent agitation.

After a whole blood has reached the seven-day expiration date, it is placed in another refrigerator

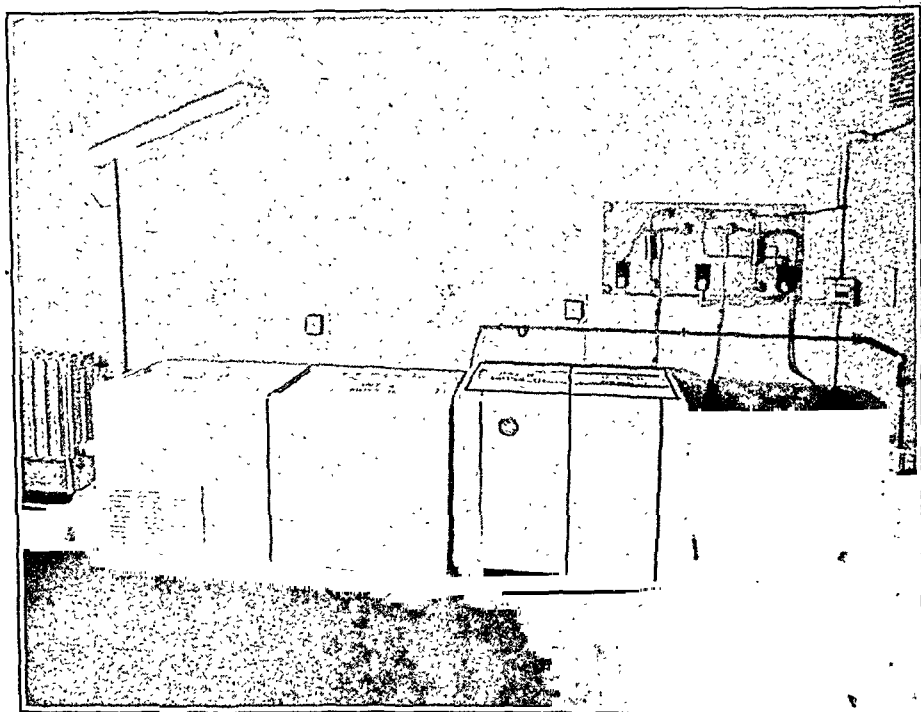


FIGURE 2. The Bottle Coolers Used for Blood Storage.

laboratory refrigerator. As soon as they are ready, they are tagged with labels of different colors for the different groups and marked with the date, the donor's name and number, the Wassermann reaction and the name of the person who did the typing. They are placed in separate compartments in the bottle coolers, which are marked and colored similarly to their tags — O, A, B and AB, respectively. The donor's card, after it has been stamped to show the blood type, the Rh factor and the initials of the persons doing the grouping, is filed in a box colored and labeled similarly to the refrigerator, the cards for the oldest bloods being at the front of the box. Furthermore, this and all other information, including the person and service for whom the blood was given, is recorded in the bank book. This is an elaborate system, but an almost foolproof one so far as errors are concerned — donors' bloods are clearly separated and marked

for conversion into plasma. The donors' cards and the bottle-tags are filed after the expiration dates and disposal of the bloods have been recorded on them.

SYSTEM OF BLOOD GROUPING AND CROSS-MATCHING

The hospital changed from the Moss to the International system of blood-type nomenclature with the opening of the bank. At the same time, there was inaugurated a careful system of double checking of all groupings and cross-matchings by having each checked by a different person. This is helpful with difficult typings and avoids the mechanical errors of using wrong test tubes and so forth. Type O, A and B testing serums are used, each one being a pooled serum obtained from three high-titer donors. The blood cells to be tested are prepared in a 2 per cent saline suspension prior to being intro-

duced into the known serums on a slide. Lecithin is placed on one slide for each grouping to prevent rouleau formation, twenty minutes in a Petri dish — to prevent evaporation — being the time required for maximum agglutination; all slides are then read under a microscope. In the rare cases in which a very sick patient or one who has had a large amount of sulfonamides is difficult to group, an incubated cross-matching is done with a thoroughly well-known — usually, professional — universal donor. In not only insisting on the system of double checking all cross-matchings and groupings but in having them done by the bank staff in so far as possible, a great

Grouping Laboratory or, more rarely, Dr. Philip Levine, of Newark, New Jersey, and with it all donors are tested. A test is also done with all patients requiring multiple transfusions or having a history of reactions, miscarriages and so forth. Dr. Levine's^{1,2} method is employed for these determinations. Cross-matchings are frequently incubated for an hour, particularly if patients have had severe reactions from Rh+ blood although positive themselves, or if they are first tested after receiving several transfusions. The charges for Rh testing are \$2, \$3 or \$4 for ward, semiprivate and private patients, respectively. An average of twenty testings



FIGURE 3. The Pooling of Plasma.

The bloods to be used are on the left. Plasma is running into the pooling flask. On the extreme right are two flasks containing diluent and ready to be filled with plasma.

measure of safety is provided, for diversification of responsibility carries the procedures into unskilled and often careless hands. An intern must have seen severe reactions in addition to possessing some knowledge of subgroups, cold agglutinins and so forth, to be able to conduct himself adequately in a blood-grouping laboratory. This is why medical students are trained to do the work at night, their work being checked by someone high up on the service — a person of known ability certified by the bank. When staff members are not present, in place of grouping and matching of the patient's blood in an emergency late at night a carefully cross-matched blood from an Rh— universal donor is used. In an extreme emergency brooking no delay, a known universal Rh— blood can be given out without cross-matching with some degree of safety. This is practically never done, since cross-matching or the use of liquid plasma is preferred for these cases.

High-titer Rh-testing serum of high specificity and stability is purchased from either the Blood

are performed each day, excluding Sundays and holidays.

PREPARATION AND STORAGE OF PLASMA

Ninety-five per cent of the plasma is drawn from bloods beyond the seven-day expiration date, and 5 per cent of it from volunteer donations. The plasma is pooled whenever there is sufficient blood on hand to do so, usually two or three times a week. The centrifuge is useful only with bloods under three days old; after that time, the cells are too fragile to withstand the 20°F. rise in temperature and concomitant agitation of fifteen minutes of spinning, which causes over one third of the bloods to show some degree of hemolysis. On certain occasions, as with the large influx of voluntary donors after the Coconut Grove fire, the yield was increased from 70 units of plasma per one hundred flasks of whole blood to 95 units by centrifuging twenty-four-hour-old blood. To make a pool, blood is selected from

all groups if possible, and never from Group O or A alone.

Prior to pooling, the air in the plasma room is sterilized by two hours of ultraviolet radiation, after which there is as little commotion and introduction of outside air as possible. The pooling of plasma is carried out as a completely sterile procedure with the workers capped, masked and in clean clothes. The operator prepares as for an operation, wearing a sterile gown and gloves. The supernatant plasma is drawn off by a needle inserted through the tubing on the bottle top, which has been previously sterilized by soaking for twenty minutes in 1 to 1000

culturing. This saves one motion and makes for one less introduction of a needle through the flask top.

Two of the culture tubes stand for a week at room temperature and two in an incubator. If two or more are contaminated, the entire pool is discarded. If one is contaminated, reculturing is done; if there is no growth the pool is used, on the theory that the original culture tube became contaminated; if there is growth it is discarded. The use of separate needles for each flask of blood or plasma, the keeping of all apparatus covered when not in use and rigid rules of preparation of sets and bottle tops (the former are autoclaved), reduces contamination.

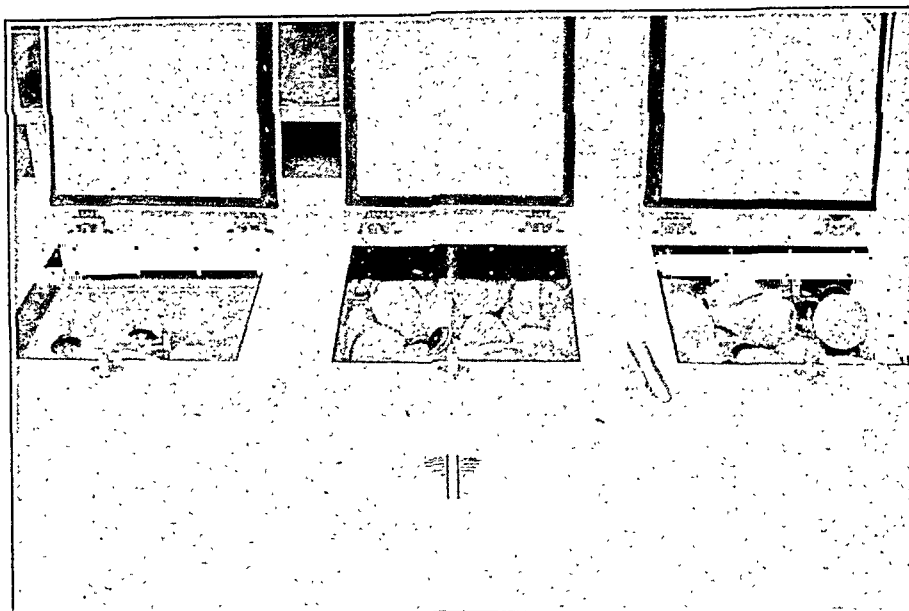


FIGURE 4. Plasma Storage Box.

The section on the left is maintained at -30°F. for quick-freezing purposes.

solution of mercury bichloride. The needle is connected to a 2000-cc. pooling flask from which the air has been evacuated. As the plasma is drawn off, it is replaced by room air through a sterile air filter. When the pooling flask is full, it is agitated and can then be cultured immediately, or it may be left undisturbed for a few days and then cultured.

Culturing, carried out according to the rules of the Office of Civilian Defense,³ is done by inserting 10 cc. of plasma deep in each of four test tubes containing 20 cc. of the aerobic-anaerobic Brewer's medium (thioglycolate broth). The pool is then drawn off into plasma flasks with a fresh needle, after which the cap and needle are removed and a permanent metal cap is put in place. The flasks contain either 250 cc. of normal saline solution or 50 cc. of 50 per cent glucose solution, freshly prepared and autoclaved. They are usually frozen immediately at -30°F. to reduce fibrin and fibrinogen-clot formation, and are stored at -10°F. or kept at room temperature. As a rule, the plasma is drawn from the pooling flasks into the final containers, a residual being left at room temperature for a day before

It has been found that connecting water suction to the flask, if the vacuum is exhausted, leads to air leaks in the connections of the set. This suction method was instituted just before the ultraviolet lights were installed, and immediately four pools of plasma were found to be contaminated. On using the lights and changing nothing else in the technic this contamination ceased. The studies on the effect of ultraviolet radiation in reducing the bacteria in room air are not complete. Exclusive of these four pools, the percentage of contamination in the making of over twelve hundred flasks of plasma is under three per cent.

We consider a plasma diluent advantageous because it cuts down on fibrin and fibrinogen-clot formation and permits much better flowing through both the filter and needle, since plasma is viscous. It also helps to prevent agglutination of the recipients' blood cells by the action of powerful anti-A or anti-B agglutinins in the plasma. Saline solution is the better of the two diluents for mechanical reasons, but may be dangerous, because of an overdosage of salt, if more than six transfusions of

plasma so diluted are given in twenty-four hours. No mercurial preservative is used because in sterile plasma no antiseptic is necessary, because the preservatives now advocated (except sulfathiazole) are poor bactericidal or even bacteriostatic agents, and because there is danger of mercurial damage to the kidneys in the use of large volumes of plasma so treated. This damage has been proved to exist, since 2 patients dying of other causes showed it at autopsy.

Most of the plasma after quick freezing is stored in thermostatically controlled refrigerators at -10°F , protected by electric thermometers and an alarm

blood is set aside ready for use. In an emergency, if an Rh typing has not been done on the patient, an attempt is made to give an Rh— blood or plasma, but we deplore unnecessary emergencies, preferring to set up bloods unnecessarily a day ahead rather than to try to do important laboratory work in a hurry at the expense of routine work. In case a blood is not called for at the time specified, the ward is called, and if the patient does not need it, it can be used for someone else, since it has not left the refrigerator.

There are two means of preventing blood from being given to the wrong patient. The first is to

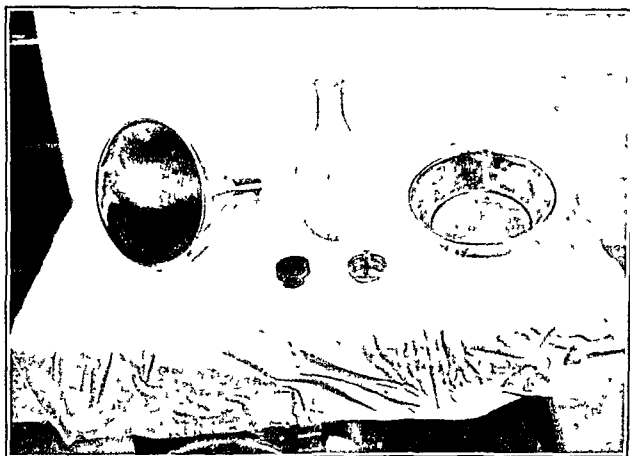


FIGURE 5 The Sterile Filtering Set.

On the right is the fine-mesh stainless-steel sieve, on the left, the stainless-steel funnel.

system. Some plasma is kept at room temperature and some, diluted with saline solution, is stored in the refrigerator. Both are ready for immediate use after negative cultures, and are useful for emergencies. We have distributed plasma to other hospitals for storage, and are equipped to give out to any hospital plasma in Fenwal flasks, with sterile glass vent tubes and rubber tubing ready for connecting to intravenous apparatus.

ADMINISTRATION OF BLOOD AND PLASMA

In requisitioning blood or plasma the physician fills out a requisition with the patient's name, number, ward, diagnosis, reason for wanting blood or plasma and the time it is wanted — usually twenty-four hours in advance — except in emergencies. This form, accompanied by 5 cc. of the patient's blood, arrives in the bank; the patient is then grouped by two persons and the oldest blood of that group on hand — on the average three days old — is selected, two cross-matchings are done, and the

have the person who is to make the transfusion come and get it, checking its tag, which has already been marked with the patient's name; the second is to let such a person take only the blood for one patient at a time. The medical services have a wise additional safeguard in the form of still another cross-matching done by the intern at the patient's bedside.

Just before the blood is given out, it is filtered through a stainless steel sieve, 14 cm. in diameter with a 0.2-mm. mesh in its bottom. It rests in a stainless steel funnel set in a flask. The whole has been autoclaved and the sieve moistened with saline solution to break the surface tension. This eliminates both large and irregular filters such as gauze or beads, or the Baxter and Cutter filter drips, which are excellent for filtering but altogether too frequently cause a reduction or stoppage of blood flow. If the blood is used immediately, the chance of the formation of a fresh plasma or blood clot is negligible. Forty-eight of these sets are kept on hand, a number well in excess of any day's transfusions.

When the blood arrives at the patient's bedside, the person administering it is supposed to check its tag with the patient's name, particularly if a nurse brought the blood from the bank. There has been some difficulty due to bloods' being improperly handled — that is, either they have been heated by some misinformed person, or after being exposed to room air in the filtering process they have been put in a ward refrigerator for a few days. Since these practices promote bacterial growth and hemolysis, we have attempted by education to eliminate them.

The fluids are administered on the private and semiprivate wards by two nurses specially trained in

always to feel for the radial pulse after application of a tourniquet. The antecubital veins are avoided in case the patient should have a protracted illness. We do not hesitate to use and have found to be satisfactory the sternal route of fluid administration. All persons, interns and nurses, are instructed in these measures and are told to sit with all patients having transfusions for the first five minutes of running, because within that time the warning of a fatal reaction usually appears. At the end of the transfusion the card attached to the bottle neck is filled out as to reaction, blood flow and so forth and returned to the bank. One per cent to 2 per cent of these cards are not returned, but by pressure being kept on the head ward nurses they are usually sent in.

In case of a reaction, the transfusion is stopped, the blood is returned to the bank for regrouping, and the patient is put on an alkalinizing regime. The urine and blood are subsequently examined for free hemoglobin.

Plasma is requisitioned similarly to whole blood, but its administration is different. It is melted in a rapidly circulating water bath at body temperature regulated by hand and checked by a thermometer. There are, however, special metal racks for the purpose of melting thirty-two units at a time in case of disaster. Plasma is administered through an intravenous set with a Baxter or fine-mesh Cutter filter inserted in the place of the usual drip bulb. Below the filter lies a three-way stopcock to permit the use of a syringe for rapid administration. This system works well; there is little clot and no stoppage of flow due to it. Furthermore, it is certain that there will be no trouble from minute pulmonary infarcts. Shortly after the inauguration of the bank, we began to use these filters on the commercial dried plasma then being administered in the hospital and cut the reactions down from a fair degree of frequency to a rare one. There are one hundred sterile filter sets on hand at all times in case of civilian disaster, such as a fire or a bombing.

There is a charge of \$25 for the plasma, the same as for blood, but we are far more liberal in giving it out to patients who can neither replace it nor repay us. This is done because plasma is considered in large measure a byproduct. In case of disaster its administration is given free.

Records and Reactions

The tags on the plasma and whole-blood flasks give the final record of what happened to the blood and are filed with the donors' cards. From time to time there are brought up to date the number of rejected donors and the reasons for rejection, the number of bloods used for plasma, the whole bloods given and the reactions. An attempt is made to find the reason for the reaction in each case, particularly in serious ones; for this purpose the facilities of the Blood Grouping Laboratory are available. To date, the percentage of reactions since the installation of



FIGURE 6. *The Administration of Whole Blood After Filtering. Note the flask of saline on the table with which the infusion was started by the intern.*

intravenous work and on the general wards by interns. This use of nurses, started as a war measure, has proved to be highly satisfactory. They can be taught a single dependable method of therapy, after learning which there is no shift to new ideas and no deviation from accepted standards of safety. Interns have been retained as fluid administrators on the wards because of the value of their learning the fundamentals of needle insertion and intravenous therapy. The nurses sharpen their own needles. They are taught to begin all intravenous administration with a saline or glucose solution and after the fluid is running well, to shift to blood or plasma. This saves both material and veins. They use, except in emergencies, the most peripheral veins first (usually those on the hand) with careful splinting of the part and good sterile technic. They are taught

the metal sieves has remained constant at 6.3 per cent. This includes 1.2 per cent of serious reactions as evidenced by high fever and chill, 1.5 per cent of minor chill and temperature reactions probably due to foreign matter in needles, bottles or tubing, 2.6 per cent explicable on an anaphylactic basis, and 1 per cent of a vague class of complaints, many of which are coincidental with, rather than caused by, transfusion. These figures are based on the first four thousand transfusions after a preliminary survey. There was 1 patient with serious post-transfusional oliguria who died on the operating table. This was thought to be a case of an anti-Rh hemolytic reaction. The death occurred prior to the present system of Rh determinations.

CONCLUSION

The methods and rules used by the blood bank of the Massachusetts General Hospital have been derived partly from the experiences of others and partly from our own experiences. They form a workable system that may, and we hope will, help other hospitals to set up blood banks or to iron out the many difficulties into which such institutions run.

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14 Technical Government

DIET IN PREGNANCY

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WARTIME rationing of foods and the difficulties encountered in purchasing a selection of unrationed foodstuffs present a serious problem from the nutritional standpoint to the pregnant woman and her developing fetus. Various surveys^{1, 2} in the past have shown relative dietary deficiencies directly paralleling economic status, but the present emergency places all women in the same category. The relation between the pregnant woman and the fetus is one of aggressive parasitism on the part of the latter, all its requirements being taken from the maternal organism. Eugenically the parturient state calls for the very best, from a nutritional standpoint, that the civilized state can present, so that the growing fetus will have available the maximum and optimum material essential to assure generations free from anomalous deficiencies of growth, as in the teeth, female pelvis and so forth, without extracting too great a toll from the parent host. It is the responsibility of the physician conducting prenatal care to make every effort to ensure the physical stamina and constitutional adequacy of the newborn infant.

The well-defined clinical syndromes of specific dietary deficiencies are too well known to require elaboration and are not common in obstetrics, although occasionally reported in the literature.³ The vast majority of deficient nutritional states, however, do not reach levels productive of a clinical syndrome, but rather present a myriad of bizarre complaints that too often are dismissed by the attending physician with a mild sedative or explained away on a psychoneurotic basis. Thus, in 84 per cent of cases Williams and Fralin⁴ found that such common complaints as nausea and vomiting of early pregnancy and easy fatigability, numbness and

muscle spasm in late pregnancy were associated with below-standard consumption of vitamin B.

It is generally agreed that the average pregnant woman engaged in domestic affairs requires approximately 2500 calories a day to carry on her increased metabolic activities.^{4, 5} This figure varies between 2000 and 3000 calories for the average woman of one hundred and twenty to one hundred and fifty pounds, depending on the state of her nutrition at the onset of pregnancy. Thus, although in the vast majority of cases it is prudent to restrict weight gain during pregnancy to 20 to 25 pounds, some women prior to conception are below average minimal standards for height and weight, and in them the parturient state with its general enhancement of metabolic activity and relief of psychoneurotic tension brings about an opportunity to correct long-standing imbalance between height and weight. The reverse is of course true in obese women, and their diets should be accordingly restricted from a caloric standpoint. Studies by Waters⁶ indicate that a weight gain of over 22 pounds is retained post partum in 60 to 80 per cent of cases, except in hydropic patients. It is of course important to distinguish carefully between hydropic and stereoplastic weight gain, both from the dietary viewpoint and from that of active prophylaxis against impending toxemia. The growth of the fetus is parasitic, and most obstetricians believe that the weight of the fetus cannot be controlled by that of the mother unless the latter be placed on starvation rations. Adair⁷ and others found the growth of the fetus to be independent of the intake of fats and carbohydrates if the total calories were adequate. Intrauterine deficiencies affecting the fetus—for example, rickets—may be produced by starvation and depletion of maternal mineral reserves, as pointed out by Maxwell, Hu and Turnbull,⁸ Rector⁹ and

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others. Sontag¹⁰ believes that scurvy tends to appear early and in a malignant form in children whose mothers suffer from vitamin deficiencies.

Attempts have been made to correlate deficient diets with the major and minor complaints of pregnancy, with results that are not conclusive at this time. Ebbs et al.¹¹ found a high incidence of miscarriage, stillbirths, prematurity and minor complications in pregnant women on deficient diets, but Williams and Fralin¹ were unable to find a direct correlation, admitting, however, that such defects might not be present until a later date when the full histories of the child and mother were available.

The essential elements in an obstetric diet are protein, fats, carbohydrates, calcium, phosphorus, iron, iodine and the vitamins. With adequate amounts of these elements all the requirements will be adequately met. Furthermore, the use of sodium chloride should be restricted.

Protein. Protein, both animal and vegetable, in quantities of 80 to 100 gm. daily, is at long last recognized as an essential for the obstetric patient. In the past, fear of kidney complications or the presence of kidney disease has caused a restriction in protein consumption, with a resultant deficiency syndrome of anemia, loss of muscle tone, edema and lowered resistance. In late pregnancy the maternal organism stores over 100 gm. of protein daily in anticipation of labor and lactation.

Fats. These are also required in quantities of 80 to 100 gm. daily and are utilized primarily for energy and for enhancing the utilization of vitamins.

Carbohydrate. This is the basic food element that allows the greatest latitude in varying consumption to control adequate caloric intake. It is estimated that 100 to 300 gm. daily is necessary to provide energy for the mother and easily assimilable food for the fetus. Whereas protein consumption may be placed at a minimal level to assure the essential elements, carbohydrate intake may be varied to suit the caloric requirement in relation to excessive weight gain. Carbohydrates are the most easily obtained food-stuffs in rationed and wartime diets, and therefore may easily assume too great a percentage of the total caloric intake. This is important, as pointed out by Becker et al.,¹² since increased amounts of thiamine chloride are necessary when the carbohydrate content of the diet is raised.

Calcium and phosphorus. Calcium intake in pregnancy should attain levels of 1.5 to 2.0 gm. daily. The calcium-phosphorus ratio and metabolism are extremely important, and failure to maintain them at desired levels leads to complaints of cramps, insomnia and headaches. Deposition of calcium in the fetal bones begins at the fourth month and continues to term, with increased demands from the seventh month on, so that at term the fetus contains approximately 24 gm. of calcium.¹³ Dental authorities do not believe that this demand on the mother is productive of tooth decay, as was formerly thought, but

it is recognized that marked calcium deficiency may lead to postpartum hemorrhage due to uterine atony. Hart and Noble¹⁴ advocate the intravenous use of calcium in such situations.

Iron. The daily requirement of iron varies between 20 and 30 mg., depending on the state of the blood at the time of conception. It has been shown by Hunscher¹⁵ that hemoglobin levels parallel adequacy of iron in the diet. The relative amount present in the maternal organism varies with changing fluid levels, but it is known that at term the placenta and fetus contain approximately 900 mg. of iron, so that the absolute demand is constant.

Iodine. In this part of the country one need not be concerned with the intake of iodine as in endemic-goiter belts, but the intake may be assured by the use of iodized table salt in selected cases.

Vitamins. The daily requirements of the vitamins are difficult to determine because of the multiplicity of their effects on the human organism. They are estimated on the basis of the smallest amount that will prevent visible and recognizable symptoms of deficiency, with an added safety factor to cover individual variations. Vitamin A is important to promote growth and fertility and for the maintenance of epithelial tissue. Its effect on visual purple is well known. It is estimated that 6000 to 9000 international units is required daily. Chief among the requirements of the vitamin B complex is that of thiamine chloride, and its adequate intake will ensure the intake of sufficient amounts of the remainder of the complex. Insufficiency of thiamine chloride is known to cause undue fatigue, loss of appetite and other gastrointestinal upsets, headaches and mild neuritis. The importance of this vitamin concerns every cell in the body rather than any one organ or system. The daily requirement varies between 1.0 and 1.8 mg. of thiamine chloride. Vitamin C requirements are met by an intake of 1500 international units or 50 to 100 mg. of ascorbic acid daily. Vitamin C is concerned with the cementing of intracellular material, and deficiencies are manifest in clinical and subclinical scurvy, the teeth, lack of resistance to infection and predisposition to brain hemorrhage in the fetus. Ley¹⁶ states that vitamin C stimulates the production of corpus luteum hormone. Vitamin D regulates the utilization of calcium and phosphorus. The daily requirement varies between 600 or 1000 international units.

Sodium. The sodium balance in pregnancy is usually positive and more than adequate for fetal needs. Restriction of sodium chloride is advisable there should at least be limitation of its use to cooking with absolute prohibition of its use at table. This is advisable both because of its relation to fluid retention and toxemia and because, as pointed out by Wadlow and Pomerance and Daichman,¹⁷ depletion of maternal salt leads to a shorter and easier labor, probably owing to dehydration of the cervix and uterus leading to more efficient and effective contraction

With an understanding of the requirements of the maternal organism and the demands made on it by the growing fetus, one can appreciate the fact that the one variable concerned is the total caloric intake. Rationing and the difficulty of securing foodstuffs are not important from this standpoint because of the ease in securing carbohydrate. Adequate supplies of the essentials are, however, at times difficult to secure, and it behooves the physician to instruct his patients concerning them, and to advise them to make every effort to obtain the essential nutrients by wise use of their rationing points. Every woman should be advised to include the following in her daily diet:

One quart of whole milk.

Two medium-sized oranges, three or four medium-sized apricots, four or five medium-sized stewed prunes or 8 ounces of tomato juice.

One egg.

Two to three servings of whole-grain or enriched bread or of cereal.

Two tablespoonfuls of butter or fortified margarine.

One serving of meat, fish, poultry or cheese, with liver or other organ meat once a week.

One or more cupfuls of fresh vegetables, including one green or yellow vegetable in addition to potato.

It is an accepted fact that foods vary in their nutritive values with storage, handling, cooking and preserving. From the standpoint of nutrition, liver is the richest of all meats in combined nutritive values. One serving of it contains more vitamin A and riboflavin than does a serving of any other natural food. It is an excellent source of iron, protein and thiamine, and even when cooked provides a fair amount of vitamin C. Vitamin B is water soluble and is readily destroyed by heat and by the addition of alkali to the cooking water. Since green vegetables and potatoes are good sources of thiamine before cooking, correct cooking practices should be used to preserve the vitamin in the cooked product. Since thiamine cannot be stored in the body, it is daily necessary to eat foods containing adequate amounts of it. Refinement is the enemy of thiamine, which is found in all living tissue; whole-wheat cereals, beans, pork, beef, liver and chicken are perhaps the richest sources. If care is taken to use whole-grain products, enriched and restored cereals, beans, peas and meats and to see that food is not overcooked, a deficiency of thiamine will not occur. Vitamin C is readily destroyed by heat; thus it is best taken in the form of raw vegetables and fruits. This vitamin, like vitamin B, is not stored in the body, is water soluble, and is readily destroyed by an alkali medium. Owing to the presence of 7-dehydrocholesterol, a fatlike substance,¹⁹ in the body and to the

effect of the ultraviolet rays of the sun, the aforementioned chemical substance is changed to vitamin D. Vitamin D is one of the vitamins that can be stored in the body, and when daily exposure to the sun and dietary intake causes the formation of more than is needed, the excess is naturally stored. With the presence of ultraviolet rays, either natural or artificial, the manufacturing and storage process is continuous. Thus, daily periods of sunning will help to attain adequate amounts of this vitamin, but the pregnant woman should supplement her vitamin D intake with one of the fish-liver oils. This may be taken in concentrated form with dicalcium phosphate, thus ensuring adequacy of the calcium intake as well as of that of vitamin D. Iron should be included in the diet in proprietary form as indicated, the actual amounts being determined by blood studies at the time of the first visit and during the last trimester.

SUMMARY

The daily dietary requirements of the average pregnant woman are reviewed, and a basic list is presented of food elements that with minimal supplemental additions will provide for an adequate normal nutritive relation between the pregnant woman and the fetus.

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CLINICAL NOTE

RUPTURE OF A LEFT TEMPOROSPHENOIDAL BRAIN ABSCESS INTO THE VENTRICLE

REPORT OF A CASE, WITH RECOVERY

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BOSTON

RUPTURE of a temporosphenoidal abscess of the brain into the lateral ventricle is an event that has rightly been considered fatal. The recording of such an occurrence by roentgenograms during life, together with complete recovery following the use of one of the sulfonamide drugs, warrants the report of the present case, especially since no similar case report has been found in the literature. With increasing use of the sulfonamide drugs it is reasonable to expect recoveries in similar cases.

REPORT OF CASE

M. K., a 56-year-old, totally blind piano tuner, was first seen on January 8, 1943. He had been blind and had had a chronic mastoiditis on the left ever since the age of 5, following an attack of scarlet fever. Ten days before consultation he developed an upper acute respiratory infection that was followed by an exacerbation of the mastoiditis. Two days before, a left-facial paralysis developed. The patient had been given 4 gm. of sulfadiazine daily for the last 3 days.

Examination showed a pulsating discharge of the left middle ear with complete left-facial paralysis. The nose, throat and right eardrum were essentially normal. There was no tenderness in the mastoid areas. The neck was somewhat rigid, and a definitely positive Kernig test was obtained. There was no sensory aphasia.

The patient was referred to the Beth Israel Hospital, where x-ray films showed a sclerosed left mastoid process with no evidence of bone destruction. A lumbar puncture showed clear fluid, with a pressure of 250 mm. of water; a cell count showed 42 fresh and 3 crenated red cells and 89 white cells, with 26 polymorphonuclear leukocytes, and 63 lymphocytes. The usual postauricular radical mastoid operation was performed on January 11. A thick cortex was found, and the antrum contained foul granulating tissue under apparent pressure. Some cells along the facial canal were broken down and filled with granulating tissue and pus. There was a small area of erosion in the area of the tegmen antri 1 cm. in diameter, which was removed. The dura in this area appeared normal except for slight thickening. Cultures of material from the mastoid area showed *Staphylococcus albus* and a nonhemolytic streptococcus. The postoperative course was normal, and there was motion of the left angle of the mouth 2 days later. Sulfadiazine was given in a dosage of 6 gm. daily, the blood level being maintained at about 7 mg. per 100 cc.

On January 15, 5 days postoperatively, there was a slight rise in the temperature and the patient appeared to be somewhat drowsy. There was a definite loss of motion in the right arm and leg. The patient was sent to the operating room and a lumbar puncture was done. This showed a pressure of 250 mm. of water; the white-cell count of the fluid was 110, with 30 polymorphonuclear leukocytes and 80 lymphocytes, and the red-cell count 74. The mastoid was reopened and the area of the tegmen antri was widely exposed, leaving an area 2.5 cm. in diameter exposing the dura in this area. The dura felt tense, and granulating tissue was present. It was incised, the brain was incised, and a cannula was inserted for a distance of 3 cm., when foul-smelling, thick, creamy pus was obtained. A semirigid rubber catheter was inserted until it seemed that the bottom of the abscess was reached. The outer part of the catheter was split and sutured

to the scalp in this area. Cultures of the pus showed *Staph aureus*, diphtheroids and a nonhemolytic streptococcus. Half an hour after the patient was brought back to his room, the stupor had disappeared and most of the paralysis of the right arm and leg had cleared. Recovery was uneventful except

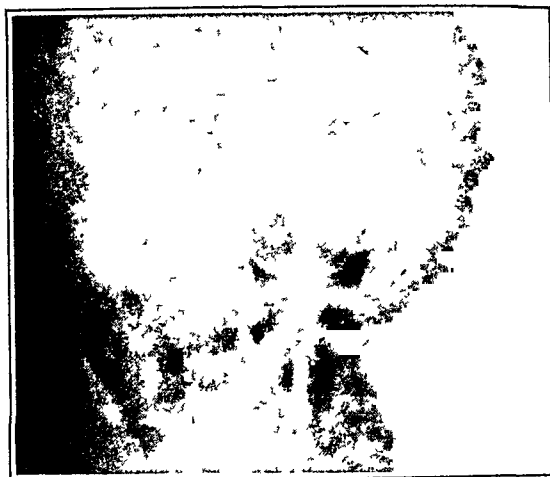


FIGURE 1. Roentgenogram Showing Lipiodol in the Sinus Tract and Left Ventricle.

for a sharp rise in temperature on January 28, at which time the temperature rose to 104°F. The dressings and catheter were changed and the sulfadiazine level, which had been maintained between 9 and 10 mg. per 100 cc., was increased by the use of sodium sulfadiazine intravenously. On the following day the sulfadiazine level was 13.9 mg. The tem-



FIGURE 2. Roentgenogram, Taken with the Patient Face Down and Showing Lipiodol in the Sinus Tract and Both Anterior Horns, and Air and Droplets of Lipiodol Scattered Through the Left Ventricle.

perature returned to normal, and the postoperative course was uneventful except for the discharge, which had become watery with a small amount of visible pus.

One week later, it was decided to ascertain the size of the cavity. At the suggestion of the roentgenologist, lipiodol (about 5 cc.) was inserted in the cavity through the catheter until there was an overflow. X-ray films were taken immediately, the report being as follows:

Asinus tract was visualized extending first in the direction of the tube. It was 0.5 cm. in width and irregular in contour. The oil had entered the inferior horn of the left ventricle from its lowermost medial aspect and it was first seen filling this lower horn (Fig. 1). After some time it

shifted throughout the ventricular system and there was only a faint coating in the left lower horn. Stereo x-rays taken in the anteroposterior and left lateral positions revealed additional facts as follows. In the face-down position, a larger amount of the oil occupied the left anterior horn. A group of droplets was seen in the right anterior horn (Fig 2). The left posterior horn was filled with

same distribution of oil (Fig. 3). There was air filling of the dilated right lower horn.

Recovery was uneventful. Further x ray films showed lipiodol at the base of the spinal column. The catheter was gradually shortened and the sulfadiazine gradually diminished. The catheter was finally removed, and the patient was discharged on February 8. X-ray films taken on March 19 showed small droplets of lipiodol in both the lower and posterior horns and along the basal cisternae. There was no evidence of intracranial air.

In May the patient returned to his work and has continued well to the present writing.

COMMENT

Abscess of the brain secondary to a chronic mastoiditis is always a grave event. Many cases go undiagnosed and terminate fatally before appropriate therapy can be given. In the present case, although the diagnosis was evident and surgery had been performed, development of sudden hemiplegia led to the diagnosis of the extension of the abscess into the brain tissue. The abscess was drained, following which lipiodol injected into the cavity showed connection of the abscess with the ventricle. It appears that the use of a high concentration of sulfadiazine probably checked further spread of the infection.

Rupture of such an abscess into the ventricle is extremely rare, and is generally seen only at autopsy. X-ray studies of such an event in life have not heretofore been made.

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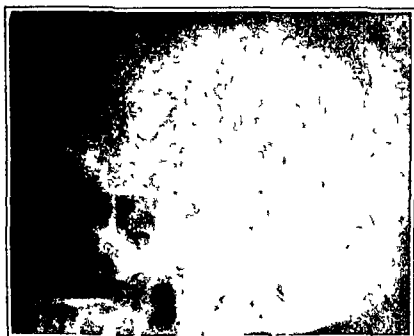


FIGURE 3 Roentgenogram Showing Lipiodol in the Anterior Horn, Posterior Horn and Sinus Tract, and Air and Lipiodol in the Temporal Horn

air, and there were several small lipiodol droplets and small air-filled spaces that could not be identified. The lateral view taken in the left position showed about the

MEDICAL PROGRESS

BLOOD BANKS AND BLOOD TRANSFUSION*

JOSEPH F. ROSS, M.D.†

BOSTON

BLOOD transfusion and the use of various blood derivatives are among the most useful and commonest forms of therapy. The recent great increase in the use of transfusion therapy has been due largely to the increasing recognition of the benefits to be derived from administration of blood or plasma in a wide variety of diseases, to the practical development of blood banks, which have made the administration of blood and plasma extremely simple and economical, and to the need of the military services for plasma and blood. Each of the numerous preparations of blood and plasma now available — unmodified blood, fresh citrated blood, blood stored in various mixtures of citrate and glucose, suspensions of erythrocytes, refrigerated plasma, frozen plasma, desiccated plasma and various preparations of purified

albumin and globulin — has certain advantages and certain limitations that make it especially useful in some conditions but unsatisfactory in others. Transfusion of blood or plasma is often of value in the following diseases: anemia; hemorrhagic diseases; hemorrhage, shock and burns; hypoproteinemia and infections. The preparations most satisfactory in the treatment of each of these conditions will be discussed, as well as the necessary precautions and the commoner transfusion reactions.

Several excellent books dealing with blood transfusion and blood banks have appeared during the last few years. Kilduffe and DeBailey¹ have thoroughly reviewed the entire literature of transfusion and present excellent practical information on the establishment and operation of a blood bank. Wiener² has again revised his classic monograph, *Blood Groups and Transfusion*, and has added valuable chapters on the Rh factor and on the use of stored blood. Mudd and Thalheimer³ have edited a collection of papers on the theoretical and practical

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aspects of blood and blood-substitute therapy that summarizes most of the important American contributions on these topics. Riddell⁴ discusses the practical details of transfusion therapy.

ANEMIA

The use of transfusion in the treatment of anemia is directed toward increasing the oxygen-carrying capacity of the blood and is achieved by supplying physiologically functional erythrocytes to the recipient. In certain cases of acute hemolytic anemia, in patients who have sustained a large and rapid loss of blood from hemorrhage, and in some acute types of bone-marrow depression transfusion is often a life-saving, emergency procedure. In certain chronic hemolytic anemias, and in patients with chronic bone-marrow depression (aplastic anemia, myelophthisic anemia, uremia and hepatic disease), transfusions may sustain life for months and occasionally years. Fortunately, the anemias most frequently encountered — iron-deficiency anemia and pernicious anemia — usually respond rapidly to iron or liver-extract therapy, and transfusion in such cases is rarely necessary, even when the red-cell count falls to levels as low as 1,000,000.⁵ Preoperative and postoperative transfusions are of considerable value in anemic patients who must undergo immediate surgery and in those in whom considerable blood loss may occur. Such transfusions aid in the prevention of shock and shorten the convalescent period.

To be successful, the transfusion treatment of anemia must provide the recipient with functional erythrocytes that will survive during the acute phase of the disease. There is little doubt that erythrocytes transfused immediately after withdrawal from a donor fulfill this requirement. Several investigators⁶⁻⁸ have demonstrated the survival of transfused erythrocytes for periods of one hundred and twenty to one hundred and thirty days, and the clinical efficacy of transfusions of fresh blood is practical proof that such cells survive during the critical periods of anemia.

Considerable controversy has arisen concerning the relative merits of unmodified blood and citrated blood for transfusion purposes.^{9, 10} Although the administration of unmodified blood is more physiologic than that of citrated blood and in skillful hands apparently produces slightly fewer reactions, it requires an exacting technic and always carries the danger of introducing blood clots or air emboli into the veins of the recipient. From a practical standpoint, the use of citrated blood is much more convenient, safer and just as satisfactory therapeutically.¹¹ Sodium citrate is relatively nontoxic, since 6 to 8 gm. may be injected intravenously during a ten-minute period without producing symptoms,¹² and larger quantities may be given over longer periods of time without ill effect. It is rapidly oxidized and excreted, 90 per cent being removed from

the blood within ten minutes.¹³ Transfusions of even large amounts of citrated blood are not likely to produce symptoms of citrate toxicity, since the citrate contained in 2500 cc. of citrated blood (6.2 gm.) is less than the toxic dose, and furthermore, considerable amount of the citrate is metabolized during the time required to administer this volume of blood.

Sodium citrate exerts little or no effect on the post-transfusion survival of erythrocytes provided citrated blood is administered to the recipient within a few hours of the time it is withdrawn from the donor.^{6-8, 14} Longer storage, however, exerts an extremely deleterious effect on erythrocytes, the post-transfusion survival of such cells varying inversely with the length of time that the blood is stored.^{7, 8, 14, 15} Eighty per cent of the erythrocytes of citrated blood stored for seven days or longer are destroyed within twenty-four hours after transfusion,^{8, 14} and consequently such blood is quite unsatisfactory for use in the treatment of anemia. Furthermore, transfusions of blood stored for too long a time may actually be dangerous because of hemolysis of the transfused cells is sometimes so rapid that hemoglobinemia and hemoglobinuria occur.^{16, 17}

Rous and Turner¹⁸ observed that the addition of glucose to citrated blood decreased its tendency to undergo spontaneous hemolysis and presumably prolonged the survival of stored cells in vivo after transfusion. The large volume (1666 cc.) of this mixture and the amount of sodium citrate (12.6 gm.) required for the preservation of 500 cc. of blood make impractical the use of this preservative, though it preserves erythrocytes fairly well.^{15, 19} During the last ten years, under the stimulus of the war and the rapidly developing civilian blood-bank services, an intensive search for better erythrocyte preservatives has been carried on in most civilized countries. The greatest stumbling block encountered in these studies has been the difficulty of assessing the value of any given preservative. Numerous in vitro studies of blood preservatives have been made, but these appear to have little positive value in indicating the probable behavior of erythrocytes after transfusion. It has now been established fairly definitely that the prevention of in vitro hemolysis, the preservation of relatively normal fragility in hypotonic saline solutions, various lytic agents, trauma, the maintenance of relatively normal potassium and phosphate concentrations within the cells and a normal pH have little significance in indicating the length of survival of stored cells after they are transfused.^{7, 15, 20, 21} Unfortunately, no investigators of cell preservatives have employed one or more of these criteria in evaluating the efficacy of their preparations, and have failed to resort to the only test that is of actual significance, that is, the survival in vivo of the stored erythrocytes after transfusion.

Attempts to determine on a quantitative basis the actual length of survival of transfused cells have been made with differential agglutinating techniques^{4-8, 15, 29} and with the use of radioactively labeled erythrocytes.^{14, 17, 30} Although both methods are subject to criticism, it is apparent from such studies that cells can be stored in glucose-citrate mixtures for at least two weeks, with an expected survival of 80 to 90 per cent of the transfused cells for at least forty-eight hours after transfusion. A glucose-citrate mixture buffered with sodium phosphate to a pH of 7.4 has been recommended by Denstedt and his associates²⁹ and appears to be one of the most satisfactory preservatives studied.

Although this preservative is satisfactory for use in civilian blood banks, it has not as yet been developed sufficiently to allow shipment of whole blood to the battlefronts. Consequently, to supply the military services with a blood substitute plasma must still be separated from blood and the erythrocytes discarded. Attempts are being made to salvage these discarded erythrocytes and to make them available for transfusion purposes. They have been resuspended in various saline and glucose solutions and administered to patients in the same way that whole-blood transfusions are given.^{31, 32} Therapeutic response to such erythrocyte suspensions has apparently been about the same as would have been achieved from administering erythrocytes preserved in citrated blood for the same length of time. Such suspensions do not prolong the allowable preservation period of erythrocytes, but they do allow the use of waste red cells from plasma-processing centers. Erythrocytes stored in blood banks are as a rule unsatisfactory for transfusion purposes by the time the plasma is separated from them, and resuspension of such old cells in the fluids so far studied cannot be expected to restore their potentiality of post-transfusion survival.

The interesting possibility exists that the breakdown products of transfused erythrocytes accelerate the production of new red cells by the bone marrow. Cruz, Hahn and Bale³³ observed that radioactive iron liberated from erythrocytes by acetylphenylhydrazine hemolysis was rapidly reutilized for the synthesis of new hemoglobin. Ross and Chapin¹⁴ found that although transfused red cells might be rapidly destroyed, the hemoglobin iron of these cells quickly appeared in newly formed erythrocytes, and the rate of reutilization of this hemoglobin iron was much more rapid than it would have been if iron alone had been given by injection. These observations suggest that even though donor erythrocytes are broken down a few days after transfusion, they may furnish easily utilizable building stones for the formation of new red cells.

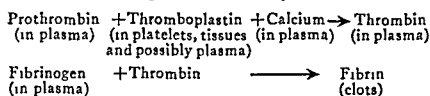
Solutions of hemoglobin have been advocated as a substitute for blood,³⁴ and Amberson and his associates^{35, 36} have been able to maintain life in cats with such solutions. The hazards associated with the

administration of the required amounts are too great to justify their clinical use, and in spite of their capacity to combine with and liberate oxygen³⁷ it is unlikely that they can ever be expected to replace or even supplement the physiologic activity of erythrocytes.

In summary, if it is desired to supply functional erythrocytes to a recipient, fresh citrated blood is probably the most desirable preparation to use, but citrated blood stored not longer than two days can be used, and blood stored in glucose-citrate mixtures for one or two weeks may also be satisfactory.

HEMORRHAGIC DISEASES

Transfusion is the only effective treatment for several types of hemorrhagic disease, and is still of considerable value in the control of several other types for which more specific therapeutic measures are now available. It is used in these diseases to supply some substance that is essential for the proper functioning of the clotting or hemostatic mechanisms but that is decreased in amount or absent in the diseased patient. The classic theory of blood coagulation is still of considerable aid in considering the hemorrhagic diseases from a therapeutic viewpoint, although it is undoubtedly oversimplified and should not be accepted too literally.



Interference with any one of these factors delays or prevents the clotting of blood, but from the practical clinical standpoint disturbances of only two of these factors — prothrombin and thromboplastin — are encountered.

Prothrombin deficiency is now known to be the cause of hemorrhagic disease of the newborn, and of the hemorrhagic states encountered in cases of biliary obstruction and of severe liver damage and in diseases of faulty absorption of fat and the fat-soluble vitamins — for example, sprue and ulcerative colitis. The anticoagulant drug dicoumarin produces its effect by depressing the formation of prothrombin. Parenteral administration of vitamin K controls many of these conditions, but it does not elevate the plasma prothrombin or control a hemorrhagic tendency if liver damage is severe.³⁸ Furthermore, the latent period before the effect of vitamin K can become manifest and decrease the bleeding tendency is occasionally too long, even in patients with normal hepatic function. In such cases transfusion of blood or plasma is the only effective means of increasing plasma prothrombin, and if administered in adequate amounts these substances will control even the severest cases of prothrombin deficiency.³⁹

It is important to remember, however, that prothrombin is a labile substance and is rapidly destroyed in alkaline solutions⁴⁰ and in blood or plasma kept at room temperatures. Prothrombin activity is lost more slowly at 4°C.,⁴¹⁻⁴³ and plasma separated from freshly drawn blood and frozen immediately maintains most of its prothrombin activity for several months.⁴⁴ Prothrombin is also preserved in desiccated blood plasma, but is destroyed during reconstitution if the reaction of the solution is not maintained near neutrality.⁴⁰ Reconstitution of desiccated blood plasma with a 0.1 per cent solution of citric acid instead of with distilled water keeps the reaction of the plasma near neutrality and maintains a satisfactory prothrombin content.

The greatly prolonged clotting time encountered in hemophilia is now known to be due to a deficiency of thromboplastin. It was formerly believed that this deficiency was due to abnormal resistance of the blood platelets, which were supposed not to break down and liberate thromboplastin in the normal fashion.⁴⁵ It now appears that a more important deficit exists in the plasma itself. Patek and Stetson⁴⁶ and Lozner, Kark and Taylor⁴⁷ demonstrated the efficacy of platelet-free normal human plasma in reducing the coagulation time of hemophilic blood, both in vitro and in vivo, and showed that plasma from hemophilic subjects contains decreased amounts of this active thromboplastin-like substance. Subsequent investigations by Taylor and his associates,⁴⁸⁻⁵⁰ have shown that normal plasma contains a so-called "globulin substance" effective in accelerating blood coagulation in cases of hemophilia. This substance is apparently quite stable and is well preserved in blood or plasma kept at 4°C. and in frozen and desiccated plasma. Injections of any of these preparations usually serve to prevent or control the hemorrhages of hemophilic patients. Purified preparations of globulin substance⁵¹ and of rabbit thrombin⁵² have also been prepared that have been efficacious as local hemostatic agents in normal as well as in hemophilic subjects.

Except for splenectomy, transfusion of fresh blood is the only procedure of specific therapeutic value in patients with thrombocytopenic purpura, and occasionally even fresh blood fails to reduce the bleeding time or to allay hemorrhage in this disease. The characteristic marked reduction of platelets does not interfere with the clotting mechanism itself, but is responsible for the failure of the clot to retract, and perhaps for the prolonged bleeding time. The exact relation between the capillary abnormality existent in this disease⁵³ and the decrease in blood platelets is obscure, but as a rule transfusion of fresh blood does increase the platelets of the recipient and decrease the bleeding time.⁵⁴ There is little difference in this respect between the efficacy of unmodified blood and that of fresh citrated blood, but injections of stored bank blood or plasma have been shown to

have little effect in controlling the hemorrhagic tendency, probably because of the rapid degeneration of the blood platelets in stored blood.⁵⁵

HEMORRHAGE

The plasma and erythrocytes lost during active hemorrhage are best replaced by transfusions of blood, although plasma may be used if the loss of red cells has not been excessive. In cases of extreme blood loss in which the hemoglobin concentration has fallen to extremely low levels blood should be used, since administration of plasma will further dilute the remaining cells and precipitate or aggravate tissue anoxia.⁵⁶ In treating patients with hemorrhage it is essential to combat or prevent reduction in the effective blood volume before active shock occurs, and transfusion must never be delayed until the blood pressure begins to fall or signs of tissue anoxia appear, since it is far easier to prevent the onset of shock than it is to treat it once it has developed.⁵⁷

The belief that transfusion of blood in cases of gastrointestinal bleeding may raise the blood pressure and actually "blow off" the clot from the bleeding site is erroneous. The rapid infusion of 500 cc of blood within five or ten minutes produces an elevation of blood pressure of only 10 mm. of mercury and Kordenat⁵⁹ demonstrated experimentally that such increase of pressure is inadequate to dislodge recently formed thrombi from small arteries. Clinical experience has also proved that the transfusion of blood in cases of bleeding duodenal ulcer is frequently a life-saving measure and does not precipitate a recurrence of hemorrhage.⁶⁰

The transfusion of unmodified blood in the treatment of hemorrhage has been advocated in the belief that it is more effective than citrated blood in promoting coagulation and hemostasis. The greater availability of citrated blood in blood banks and the rapidity and ease with which such blood can be procured and administered in cases of emergency appear to outweigh the slight advantages claimed for unmodified blood.⁵⁸ Theoretically, fresh blood may be more effective than stored blood because of the degeneration of platelets and prothrombin in the latter, but practically, stored blood is quite satisfactory.

Bleeding into the pleural or peritoneal cavity may be so excessive that shock is produced. Active transfusion — the transfusion of this blood into the patient's veins — has been suggested as an emergency procedure.⁶¹ The mortality from such transfusions has been between 2 and 4 per cent,⁶¹⁻⁶³ due usually being attributable directly to infusion of contaminated blood or of blood that has remained in the peritoneal cavity for seventy-two hours or longer. Because of the danger of the procedure it should be employed only in cases of extreme emergency when other blood or plasma cannot be obtained.

(To be concluded)

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 30061

PRESENTATION OF CASE

A twenty-three-year-old woman was admitted because of swelling in the lower back of three months' duration.

The patient had been in excellent health until about eight months before entry, when she developed pain in the lower midback. This was severe only when she tried to bend, and it did not radiate. It lasted for about five months, improving slowly but steadily. Three months before admission she noted the gradual onset of swelling in the lower midback. The swelling increased in size, but there was no pain. She had no weakness in the back or legs or any other symptoms.

One sister had arrested tuberculosis.

Physical examination showed a well-developed, well-nourished girl in no distress. The heart was normal. Slight "wheezes" were heard in the right lung. The abdomen was normal. A cystic, fluctuant, soft mass measuring about 15 cm. in diameter was found in the midlumbar region. No neurologic abnormalities were noted.

The blood pressure was 100 systolic, 80 diastolic. The temperature was 98.6°F., the pulse 90, and the respirations 20.

Examination of the blood showed a white-cell count of 11,300. The hemoglobin was 12.8 gm. per cent. The urine was negative. A blood Hinton test was negative, and a blood Wassermann doubtful. A lumbar puncture showed initial pressure of 120 mm. of water, with normal dynamics. Forty centimeters of clear fluid was withdrawn, which contained 3 white cells and no red cells per cubic millimeter; the total protein was 24 mg. per 100 cc., and the gold-sol curve 0000000000. A Wassermann test was negative. Pressure on the tumor gave no rise in the manometer.

Roentgenograms of the spine showed destructive changes in the dorsal portion of the spinous process of the fourth lumbar vertebra. This spinous process was enlarged and appeared to extend into the area of the fourth lumbar vertebra. There was no evidence of involvement of the neural arch, aside from the spinous process. The fifth lumbar vertebra was intact. An air myelogram with the air column poorly outlined in the lateral but clearly visible in the anteroposterior view. It was visualized only below the level of the fourth lumbar vertebra. The nerve sheaths were not filled. The cul-de-sac extended to the level of the second sacral segment and was normal in appearance. There was failure of closure of the spinal canal below the third sacral segment. No connection could be seen between the spinal canal and the mass posterior to the sacrum on the right side.

On the tenth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JAMES B. AYER: We are not told at what levels the lumbar puncture and the air myelogram were done.

DR. JOST MICHELSEN: They were both done at the same time. The needle was put in the interspace between the second and the third lumbar vertebra.

DR. AYER: Apparently there were two destructive areas, one in the lower sacral region and one in the spinous process of the fourth lumbar vertebra. Perhaps we should see the x-ray films.

DR. LAURENCE L. ROBBINS: These films were taken at the time of the air myelogram but with a different technic from that which would best demonstrate the soft-tissue mass. I think we can make it out in this area. It apparently extends from about the posterior margin of the spinous process of the second lumbar down to approximately the second sacral segment. There is definite destruction of the spinous process of the fourth lumbar vertebra, which is apparently at about the center of the mass. I do not believe that this is a congenital anomaly, but rather a destructive process. So far as the air myelogram is concerned, it is not a satisfactory examination. I do not see any evidence of an inflammatory process encroaching on the spinal canal. There is evidence of congenital anomalies. The sacral hiatus is larger than usual, and there is incomplete fusion of the laminae of the first sacral segment, as well as an anomaly in the development of the articular facets of the third lumbar vertebra; but these things are of no practical importance.

DR. AYER: In the transcription it says that the air column stopped below the fourth lumbar vertebra. Is that your interpretation?

DR. ROBBINS: As I said before, the air myelogram was unsatisfactory; but I think that there was air all through the lumbar canal. The only way one could be sure would be to stereoscope these films in the anteroposterior view.

DR. AYER: Then the dogmatic statement "It was visualized only below the level of the fourth lumbar vertebra" is not borne out.

DR. ROBBINS: That is someone's opinion who had the opportunity to stereoscope the films. I should think there was air going up to the first lumbar vertebra.

DR. AYER: A good deal depends on this point, and I should like to say that the experience of some of us with air myelograms has not been entirely satisfactory. I prefer lipiodol. On the other hand, the members of a good many other clinics believe that they can outline a disk, which is something smaller than what we have here. So there is a difference of opinion in the interpretation of air myelograms.

We are told that the physical and neurologic examinations were negative, except for a lump the size of a grapefruit in the midlumbar region. Therefore discussion must center primarily on this mass. It was said to be cystic and fluctuant, and there was no pain connected with it, except when she bent her back. It enlarged rapidly, although we need not assume that its growth was limited to three months — perhaps eight months is a more reasonable estimate. As no note is made we may perhaps assume that the mass was neither tender, discolored nor warm to touch. Nor are we told whether it was attached to the skin or deep structures.

From the evidence, I think we can safely say that we are concerned with a rapidly growing mass situated slightly to the right of the midline in the low lumbar region, which contained fluid but was non-inflammatory, and was not accompanied by gross destruction of the vertebrae. Therefore, we can eliminate both pyogenic and tuberculous abscess, and also cancer originating in a vertebra. Tumors such as sarcoma and neurofibroma are firm and resilient, not primarily cystic, and may also be eliminated. By far the commonest fluctuant mass in this region is the meningocele, and the description given suggests this, although I miss the presence of the characteristic dimpling of skin and lanugo hair so characteristically seen. Nor is it likely that a meningocele, and even more likely a meningomyelocele, would be present with no disturbance of nerve function, particularly weakness and deformity of feet and bladder incontinence. Nor was there the characteristic lumbar defect in the spine. Nor was there fluid in this mass that connected with the subarachnoid space. I am forced to consider the embryonal tumors that occur in this region. Chordoma, which I believe is always firm and gives a characteristic x-ray picture of wide, clear-cut destruction of the sacrum, seems unlikely. But dermoid cyst and perhaps lipoma seem to answer the characteristics given. Both are associated with imperfections in the spine.

Was the spinal canal invaded? From the original interpretation of the air myelogram we are led to believe a block existed at the level of the fourth lumbar vertebra, but review of the films by Dr. Robbins fails to confirm this interpretation. Certainly there was no clinical evidence of involvement of the cauda equina, and yet we have often seen the lumbosacral canal filled with tumor — especially lipoma — without clinical evidence of its presence.

I therefore believe that the diagnosis that best fits this condition is a dermoid cyst, probably but not

necessarily with attachment to the meninges through the imperfect spine; lipoma is my second choice.

DR. MAURICE FREMONT-SMITH: May I ask whether cold abscess starting in the spine might not make this picture? You mentioned it, but you then hastily discarded it.

DR. AYER: I threw it out rapidly and did not give all the reasons. I think it is fair to assume that the mass had been there for eight months and, if tuberculous, should have shown more spinal destruction than it did. Does not Pott's disease start from the body rather than from the spinous process? Nor do I remember seeing it in the lumbosacral region. There was no fever. A sister had tuberculosis, but not the patient. Perhaps I threw out tuberculosis too nonchalantly but I do not believe that it is likely.

DR. ROBBINS: Is destruction of the spinous process frequent in lipoma or dermoid?

DR. AYER: Not in lipoma. In dermoid cysts, however, I believe that there are rests in the spinous processes as well as in the lateral masses. That is a point in embryology of which I am not sure.

DR. ROBBINS: Yes, I think there can be; but the thing that is impressive here is that it appears to have been a destructive process and not an erosive one.

DR. AYER: That is the weak point in the argument.

DR. ROBBINS: I should expect to see erosion of the spinous process.

DR. AYER: I rather wanted to have it a developmental defect. Perhaps it is unreasonable to say that I still wonder if it could have been originally a developmental defect because of the other anomalies that you have demonstrated. If I could have that leeway it satisfies me. Certainly an osteomyelitis starting there would not give this picture.

DR. ROBBINS: It could give that appearance in the spinous process.

DR. AYER: Yes, but hardly the rest of the picture, with the normal temperature and so forth.

DR. BENJAMIN CASTLEMAN: Dr. Kubik saw this patient before operation.

DR. CHARLES S. KUBIK: I do not remember the case well except that I missed the diagnosis. Perhaps Dr. Michelson remembers it.

DR. MICHELSEN: Several points were not brought out in the summary that perhaps would have been of some value to Dr. Ayer. First of all, the size of the tumor increased on straining, sneezing and coughing, which made it fairly evident that the tumor contained fluid; but it did not transilluminate. There was also some tenderness to palpation.

It was decided to do an air myelogram not so much because we were hunting for an obstruction or a tumor in the spinal canal, but because we wanted to find out whether the mass was connected with the subarachnoid space. When this decision was made the destruction of the spinous process of the fourth lumbar vertebra had not been reported. The first x-ray films were read as negative.

On biopsy of the tumor a large amount of greenish pus was obtained and a small piece of bone was found at the bottom of the abscess.

CLINICAL DIAGNOSIS (preoperative)

Tumor of lower back (? hemangioma).

DR. AYER'S DIAGNOSIS

Dermoid cyst?

Lipoma?

ANATOMICAL DIAGNOSIS

Tuberculosis of spinous process of fourth lumbar vertebra.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The material we received showed caseous tuberculosis.

DR. MICHELSEN: After the diagnosis of a cold abscess was established, Dr. George W. Van Gorder was called in consultation. He stated that he had seen a similar lesion in that location, but that the condition was extremely rare. A detailed clinical checkup revealed that the patient had incipient tuberculosis of the lungs, and she was discharged to a tuberculosis sanatorium.

DR. AYER: The "wheezes" meant something after all.

CASE 30062

PRESENTATION OF CASE

A sixty-three-year-old tool inspector entered the hospital because of severe pain in the anterior chest of four months' duration.

The patient was in good health until about ten months before entry, when he developed a severe, dry cough and "bronchitis," which caused nausea and occasional vomiting. The cough persisted and was productive of small amounts of white mucous material. Syrup of hydriodic acid gave no relief. There was no hemoptysis, fever or night sweats. Shortly after the onset of the cough, his voice became hoarse, and gradually became worse, until on admission he could only whisper.

Four months before admission he experienced the sudden onset of a sharp, stabbing, substernal and epigastric pain, most pronounced after coughing. It recurred as often as six times a day and was occasionally made worse by deep inspiration. The pain was controlled by medicine that contained a "lot of codeine." Two months before admission he noted progressive weakness of the arms and legs. He had difficulty in keeping his balance and in walking and fell on an average of four times daily. There was urinary urgency without other urinary symptoms. Shortly thereafter he developed constipation, followed by periods of fecal incontinence, occurring about twice a week. There was no distention or

melenas. One month before entry he developed exertional dyspnea without orthopnea or paroxysmal nocturnal dyspnea. Two weeks before admission he felt as though he had gone to sleep from the chest pain. He attributed this to too much codeine since after omitting the drug this disappeared to some extent. His chest pain also decreased in severity. Nevertheless he was forced to give up his job. His appetite had remained "perfect," but there was a weight loss of 30 pounds in the six months preceding entry. He developed several boils.

Physical examination showed a moderately emaciated, slightly dyspneic man who coughed occasionally and spoke in a whisper. The skin was dry. There were a large ecchymotic area over the right knee, and an area of redness, swelling and ulceration over the left wrist. A fluctuant furuncle was present on the left hand. The tongue displayed a coarse tremor. The gag reflex was active. The trachea deviated slightly to the right. There was slight tenderness below the angle of the right scapula. A respiratory friction rub was heard in the right axilla. The diaphragmatic excursion was limited. The border of cardiac dullness was 10.5 cm. from midline in the sixth space. The sounds were of normal quality and regular. The pulmonary second sound was greater than the aortic. There was a slightly tender mass in the epigastrium according to one observer, and no masses or tenderness according to another. Rectal examination was negative. Neurologic examination showed hyperactive patellar and ankle jerks, unsustained ankle clonus bilaterally and weakness of both lower extremities, more noticeable on the right. The upper extremities were weak. There was atrophy and wasting of all muscles of the extremities. The vibratory sense was diminished at the toes and ankles, and the position sense was absent in the toes. Hypesthesia and hypalgesia extended to the level of the umbilicus on the left, and to slightly lower than this on the right. The touch sense appeared to be intact. Laryngeal examination was unsatisfactory. The left tip of the epiglottis was ulcerated. The arytenoids and the pyriform sinuses were swollen and reddened. Both arytenoids motionless. The cord could not be visualized.

The blood pressure was 168 systolic, 92 diastolic. The temperature was 102.6°F., the pulse 82, the respirations 28.

Examination of the blood showed a red-cell count of 4,400,000, with 10.5 gm. per cent of hemoglobin. The white-cell count was 11,750, with 78 per cent neutrophils. There was the slightest possible trace of albumin in the urine. The stools were guaiac negative. A blood Hinton test was negative. The vital capacity was 35 per cent of normal. No sputum examination was recorded, but a smear of the gastric contents showed no tubercle bacilli.

X-ray examination of the chest showed a large, coarse, nodular miliary process involving both lungs (Fig. 1). In addition there were plaque-like areas

of increased density in the central portion of the left chest and in the upper lung fields. At the apices, honeycombing and fibrosis were seen surrounding a few small cavities. The heart was enlarged, and the aorta moderately tortuous. Diaphragmatic motion was limited, and the costophrenic angles were obliterated. A gastrointestinal series and a barium enema were negative. X-ray films of the dorsolumbar spine and pelvis showed a destructive process involving the inferior aspect

DIFFERENTIAL DIAGNOSIS

DR. MAURICE FREMONT-SMITH: This is the case of a sixty-three-year-old man who had apparently been in good health until ten months before entry, at which time he developed cough and hoarseness. Bronchiogenic carcinoma is the first thing to think of when at this age a man's illness begins with cough. He might have had a primary bronchiogenic carcinoma with metastases into the other lung and



FIGURE 1. Roentgenogram of Chest.

of the body of the fourth dorsal vertebra and the upper aspect of the body of the fifth dorsal vertebra, with involvement of the disk. In the anteroposterior view there was a questionable soft-tissue mass surrounding these vertebrae. No other evidence of a destructive process was seen. A lumbar puncture gave an initial pressure of 270 mm of water; 10 cc of clear colorless fluid was withdrawn, the final pressure being 110 mm. The fluid contained 47 red cells per cubic millimeter, but no white cells. The total protein was 63 mg. per 100 cc. The gold-sol curve was 0000122100. The level at which the needle was inserted is not stated in the record, but there was no evidence of blockage.

The temperature remained about 103°F. The patient became more confused and delirious, and died on the eleventh hospital day.

with a metastatic process in his spine, causing cord changes. Against this is the fact that it is very unusual for a metastatic carcinoma in the lung to form a cavity. Such an explanation would also leave out entirely the changes in the larynx, and if one takes those into consideration the other possibility, which seems by far the most likely, is tuberculosis, which not infrequently becomes active in old age.

This patient apparently had widespread tuberculosis of both lungs and a metastatic tuberculous process in the spine, with a Pott's abscess and laryngeal tuberculosis. He could, however, have had primary laryngeal carcinoma with metastases or primary carcinoma anywhere in the body with metastases. It should be noted that intrinsic carcinoma of the larynx — that is, carcinoma of the vocal cord — does not metastasize rapidly and the

metastases do not occur below the clavicles. Extrinsic carcinoma of the larynx, like any other carcinoma, can metastasize to any part of the body.

The fact that this man had an ulcer on the epiglottis is greatly in favor of tuberculosis. If this process was tuberculous, it is surprising that the patient did not have pain on swallowing and that pain in the larynx was not mentioned.

It is worth while to emphasize two things before going on with the differential diagnosis. In the first place, one is apt to forget that pulmonary tuberculosis can start with hoarseness and not with cough. Secondly, just as we have had impressed on us during the last few years that chronic edema of the legs is not always cardiac, and that a large proportion of patients have edema from other causes, frequently from varicose veins, so too in dealing with chronic dyspnea one is not apt to realize that the dyspnea may come not from the heart but from other trouble in the thorax.

This man also had injury to the cord. Manifestly the pyramidal tracts were involved, with increase in the reflexes and a little clonus, as well as the posterior tracts, with sensory disturbance. The thing that disturbs me is that the muscles of all the extremities were said to be atrophic. The patient could have had atrophy of the legs from the cord injury, especially if the anterior-horn cells were injured by compression. To explain the atrophy of the hands a cervical lesion must have existed, or one would have to premise a generalized disease, such as myotrophic sclerosis, which is farfetched.

Did the boils indicate that there was a secondary staphylococcal blood-stream infection on top of the primary infection, which I believe was tuberculosis? I have gone ahead without looking at the x-ray films and may have to modify some views when I see them.

DR. LAURENCE L. ROBBINS: There is a rather sharply defined mottled process completely involving both lungs. I am not at all sure that I can be positive about the presence of cavities. With this type of process it is a rather difficult decision to make, because numerous superimposed miliary nodules, when taken all together, give an impression of cavities. Certainly there are areas of rarefaction that do suggest small cavities. If there are cavities, I should have expected them to be higher in the right upper lobe.

The films of the spine show destruction and compression of the bodies of the fourth and fifth thoracic vertebrae. The disk spaces are not well visualized and there appears to be a surrounding soft-tissue mass.

DR. FREMONT-SMITH: Is it fair to ask whether this picture in the lungs was miliary tuberculosis on top of old tuberculosis of the lung?

DR. ROBBINS: It is hard to be sure that there was an old tuberculous process. It is a question to ask, but I do not see how I can answer it. There are

certain things, such as a thickened pleura, that may be the result of an old process. The miliary process can be due to several different things from the x-ray standpoint.

DR. FREMONT-SMITH: How about silicosis?

DR. ROBBINS: It might be, but it is atypical. Miliary malignant disease can give a similar x-ray picture.

DR. FREMONT-SMITH: Would you say that it could not be miliary tuberculosis?

DR. ROBBINS: No; that is probably the commonest condition to produce such an appearance.

DR. FREMONT-SMITH: I think that the evidence, including the laryngologic examination, the destructive process in the spine, the soft-tissue mass and the x-ray picture, is in favor of a diagnosis of tuberculosis. The sputum was not examined. The gastric contents were said to be negative. I am rather dubious about the value of gastric contents unless the material is put into a guinea pig, in which case one gets a reasonably accurate diagnosis. That should always be done in a case of probable pulmonary tuberculosis that is not diagnosable by sputum examination. I shall rest my case on the diagnosis of tuberculosis.

DR. BENJAMIN CASTLEMAN: Dr. Means, you saw this patient, will you give us your impression?

DR. J. H. MEANS: Our line of reasoning followed much the same course as that of Dr. Fremont-Smith. We were confronted with a spinal lesion, — compression of the thoracic cord with certain neurologic manifestations resulting therefrom, — and this peculiar lung lesion, with fever. We thought that it was either cancer or tuberculosis, but we did not know which. I tried to pin down the radiologist, but did not succeed. I asked him the following questions: "Can you say definitely that the spinal disease is or is not tuberculosis? Can you say definitely that the spinal disease is or is not malignant? Can you say definitely that the lung lesion is not miliary tuberculosis?" He wrote in answer to all my questions, "No"; but he did favor tuberculosis.

DR. FREMONT-SMITH: Might I ask Dr. Kubik to say a word about my comment on the neurologic findings — that is, how to account for the atrophy of the arms and legs.

DR. CHARLES S. KUBIK: There is definite evidence of cord compression, because of the changes in the leg reflexes and the sensory impairment below a certain level, but I do not believe that we know enough about the atrophy in the arms to be able to say anything about it. That might have been due to the generalized weight loss.

DR. JOST MICHELSEN: Dr. Robbins, do you think the involvement of the disk is in favor of tuberculosis rather than of malignant disease?

DR. ROBBINS: Yes, if I could be sure the disk was involved. A study of that area of the thoracic spine is particularly difficult because of the curvature,

d I am not sure that it is not simply a process of overlapping shadows rather than of active destruction of the disk.

CLINICAL DIAGNOSIS

Carcinomatosis of lung and spine?
Miliary tuberculosis?

DR. FREMONT-SMITH'S DIAGNOSES

Miliary tuberculosis, involving lungs, spine and larynx.

Healed pulmonary tuberculosis.

ANATOMICAL DIAGNOSES

Miliary tuberculosis of lungs, spine, meninges, larynx and kidneys.

Healed pulmonary tuberculosis.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy on this man showed a widespread miliary tuberculosis, with a cavity 4 cm. in diameter in the right upper lobe. There was tuberculosis in practically every organ in the body. The fourth and fifth dorsal vertebrae, with the intervening intervertebral disk, were involved in a large tuberculous abscess. We were not sure on gross examination whether there was actual invasion of the meninges, but microscopically there is not only involvement of the meninges locally but also involvement of the ependyma of the ventricles, apparently an ascending infection. There was tuberculous ulceration of the larynx.

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COMPARATIVE VALUES

WE Americans, with our mixed racial strains, our varied hereditary characteristics drawn from many lands and many ethnologic types, have attained at least one common factor — acquired, perhaps, from an environment that has been overly generous to us. We are generous to others, particularly if a call is made in a way to appeal to our open, warm-hearted, somewhat erratic and at times exceedingly sentimental emotions. If anyone tries to take what belongs to us, we fight at the drop of a hat; but if the emotional floodgates are opened, we give it away. This characteristic is simply illustrated by the old story of the tough character and the flower girl: "Don't cry, little girl. I'll buy your — — violets."

The journalistic gentry learned long ago to pluck the pulsing heartstrings of their public. Crime may go unpunished and injustice may pile unnoted upon injustice, but let some columnist mention the fact that a cripple needs a wheel chair or a veteran requires a wooden leg, and the checks float down like a kindly Christmas snowstorm. The need must be specific and emotionally presented, the beneficiary must be an individual with a personality of sorts, but the response is hundredfold, if it is only a new wig that is requested.

Publicity (or propaganda, if you will) is one of the most powerful instruments that we possess, and a great trust — to use it well and wisely — is put into the hands of those who guide it.

We have seen recently an example of its effectiveness, regardless of how wisely or unwisely it was in this case directed, or whether it was initiated in the best interests of the public. A child suffering from an admittedly incurable chronic nephritis (presumably nephrosis) has had life maintained, or at least has been treated, by the administration of large quantities of blood plasma, the fluid for lack of which many an American soldier may be doomed to die this summer unless the American public is re-awakened to its duty. A Boston newspaper, taking up the cause of the child, has obtained enough plasma from local donors to guarantee, it is said, some prolongation of life for the patient.

If journalism will now turn its considerable powers toward obtaining enough blood donors for the Red Cross to make up the deficit of plasma that threatens the effective treatment of our wounded soldiers and sailors, we shall congratulate it most wholeheartedly on the gesture it has made in behalf of the child.

TRENDS IN PNEUMONIA MORTALITY

Most physicians are greatly impressed by the improved outlook with respect to pneumonia. This favorable impression is derived from the better prognosis in individual cases of bacterial pneumonia under modern chemotherapy. Some recent studies, however, indicate that the trend in pneumonia mortality may be changing for the worse, although

it is hoped that these changes will be only temporary.

A recent survey by the United States Public Health Service¹ indicates that since the summer of 1937 pneumonia mortality has markedly declined. An average of the mortality rates for the five-year period 1938-1942 compared with that of the five preceding years showed a decline of approximately 40 per cent, and the decline occurred in all geographical sections of this country. The mortality from influenza and pneumonia for a group of ninety cities in the United States, however, was higher in the third and fourth quarters of 1942 and the first quarter of 1943 than it was in the same quarters of the three preceding years.

Epidemics of minor intensity occurred in five of the eight winters since 1935. Three of these epidemics — (1935-1936, 1936-1937 and 1940-1941) — were practically nationwide. The epidemics of the winters 1938-1939 and 1939-1940 were confined to four or five geographical sections of the country.

An increase in pneumonia mortality was also noted in the latter months of 1942 and the early months of 1943 among the industrial policyholders of the Metropolitan Life Insurance Company.² The Metropolitan statisticians noted a sharper than usual rise in the death rate from pneumonia during the winter of 1942-1943, which was much higher than the rise in the corresponding months of the previous year. They believe that this was due chiefly to an increase in the virus or atypical pneumonias, which fail to respond to sulfonamide drugs. They also noted that a large proportion of the fatal cases of the virus pneumonia occurred among young persons. Thus, in 36 per cent of the deaths from this type of pneumonia the patients were between fifteen and forty-four years of age, as compared with the usual figure of 18 per cent. Their data indicated that pneumonia during this period was two or more times as frequent in the Army as in the preceding year and that in some defense areas pneumonia was more than three times as frequent early in 1943 as it was in 1942. In spite of all this, the mortality was still 35 per cent lower than in the first quarter of 1938-1939.

Another interesting review of the public-health and economic aspects of pneumonia was recently published by workers of the Equitable Life Assur-

ance Association of the United States.³ They compared experience among a large group of industrial employees in the pre-sulfonamide years 1935-1937 with that for the period from January 1, 1939, to June 1, 1942. Most striking was the reduction in the case fatality rate in pneumonia from an average of 20.8 to 3.9 per cent in this short space of time. In addition there was a decrease in the total duration of illness from the modal (most frequent) period of thirty-eight days in 1935 to twenty-seven days in 1941. According to their calculations the lives of twenty-five thousand workers were saved annually, and in addition the loss of a million working days was prevented as a result of the shortening of the period of illness. These authors noted that the incidence of pneumonia increased appreciably during the period of study. They believe that factors such as congestion in industrial areas incidental to the war effort might have been responsible for this increase.

It is well known that deaths from pneumonia increase during periods when influenza is epidemic. Such an increase in pneumonia deaths was associated with the widespread epidemic of influenza in 1940-1941, although this increase was not of alarming proportions. Although the general upward trend of pneumonia mortality during the first part of 1943 did not continue throughout the year,⁴ another increase did occur during the latter part of the year as a result of the prevalence of influenza. In New York State, excluding New York City, the number of pneumonia cases reported for the week ending January 1, 1944, was 982.⁵ For the week ending January 2, 1943, only 397 cases were reported, and this compares with the 1938-1942 average for the similar period — namely, 358 cases. The reporting of cases of pneumonia is, of course, not accurate and is not required in many states. There is no doubt, however, that the number of primary pneumonias in Massachusetts has increased — perhaps in a similar proportion. In the large hospitals in Boston the great majority of these have been pneumococcal lobar pneumonia.

Whether further increases in pneumonia deaths will occur apart from the epidemic rise remains to be seen. At any rate these recent observations should dispel the feeling of complacency that has

been engendered by the individual successes due to improved therapy. Facilities are still available for pneumococcal typing in Massachusetts, but physicians are not availing themselves of these facilities to a sufficient extent. Many of the recent cases were of great severity, and a significant proportion of them were suitable for combined chemotherapy and specific antipneumococcus serum therapy. Physicians may well benefit from a greater use of the bacteriologic facilities that the Commonwealth and various communities offer to aid in the proper therapy of pneumonia.

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MEDICAL EPONYM

SCHILDER'S DISEASE

This eponym refers to a form of encephalitis first described by Dr. Paul Schilder (b.-1886), while a teaching assistant of the Royal Psychiatric Clinic in Leipzig, in a paper entitled "Zur Kenntnis der sogenannten diffusen Sklerose: Über Encephalitis periaxialis diffusa [Contribution to the Study of So-called Diffuse Sclerosis: Encephalitis periaxialis diffusa]," which was published in the *Zeitschrift für die gesamte Neurologie und Psychiatrie* (10:1-60, 1912). A portion of the translation follows:

There is a diffuse affection of the white substance of the hemispheres in children that we are justified in regarding as a disease entity on the basis of characteristic macroscopic and microscopic findings in the brain. I propose for it the designation "encephalitis periaxialis diffusa."

The clinical picture of this disease is extremely variable. It follows a course which sometimes resembles that of brain tumor, sometimes simulates multiple sclerosis, or again resembles Heubner's diffuse sclerosis. We may suspect the existence of this disease if symptoms point compellingly to a widespread lesion involving both hemispheres. Attacks with the symptomatology of multiple sclerosis running a rapid course in youthful patients will likewise bring our disease to mind. The disease is a fatal one, with little tendency to remissions.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

TREASURER'S OFFICE

The bills for \$10.00 recently forwarded to all members of the Society cover the regular annual dues ("assessment") for membership in the Massachusetts Medical Society. The insert describing the Postwar Loan Fund is purely informative regarding future plans. The current assessment is *not* for the Postwar Loan Fund.

ELIOT HUBBARD, JR., *Treasurer*

DEATH

SPALDING — Fred M. Spalding, M.D., of Brookline, died January 24. He was in his seventy-fourth year.

Dr. Spalding received his degree from Harvard Medical School in 1897. He practiced in Boston for many years and served as an intern and later senior ophthalmic surgeon and consultant to the Massachusetts Eye and Ear Infirmary. He retired from active service in 1924, but returned after the start of the war to give his service as an aid to the war effort. He was a member of the Massachusetts Medical Society, American Medical Association and American Ophthalmological Society. He was a former president of the New England Ophthalmological Society.

His widow, two sons and a daughter survive.

NOTICES

BOSTON MEDICAL HISTORY CLUB

There will be a meeting of the Boston Medical History Club in Sprague Hall at the Boston Medical Library, 8 Fenway, on Monday, February 21, at 8 p.m. Dr. Louis E. Phaneuf will speak on the subject "J. Marion Sims — Father of Modern Gynecology."

All interested persons are cordially invited to attend this meeting.

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, February 15, at twelve noon.

Dr. Brainard F. Conley will discuss the Wagner-Murray-Dingell Bill. This proposed legislation (known as Senate Bill 1161 and House Bill 2861) has provoked much discussion in medical and hospital associations and is of interest to every physician.

Physicians are cordially invited to attend.

SUFFOLK CENSORS' MEETING

The censors of the Suffolk District Medical Society will meet for the examination of candidates at the Boston Medical Library, 8 Fenway, on Thursday, May 4, 1944, at 4:00 p.m. Applications must be received not later than February 15.

NEW ENGLAND PEDIATRIC SOCIETY

There will be a meeting of the New England Pediatric Society on Wednesday, March 8. The clinical presentation will be held at the amphitheater of the Children's Hospital, and all other events at Longwood Towers, Brookline.

PROGRAM

- 4:00 Clinical Meeting: Presentation of cases by members of the Children's Hospital Staff.
- 6:30 Refreshments.
- 7:00 Dinner.
- 8:00 Annual meeting.
- 8:15 Neurosurgical Problems of Childhood. Dr. Francis D. Ingraham.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The regular meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston, on Wednesday, February 16, at 8 p.m. The topic for discussion will be "The Technic and Results of the Kenny Treatment." Miss Dorothy Fredrickson will discuss and demonstrate the Kenny technic. A council meeting will be held at 6 p.m., followed by an informal dinner in the Empire Room at 6:30.

All members of the medical profession are invited to attend this meeting.

(Continued on page xiii)

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ELECTROMYOGRAPHIC STUDIES OF MUSCLE DYSFUNCTION IN INFECTIOUS POLYNEURITIS AND POLIOMYELITIS*

MARY A. B. BRAZIER, Ph.D.,† ARTHUR L. WATKINS, M.D.,‡ AND
LIEUTENANT COMMANDER ROBERT S. SCHWAB (MC), U.S.N.R.§

BOSTON

THE similarity of clinical findings in acute infectious polyneuritis¹ and in poliomyelitis and the difficulties in differential diagnosis have recently been emphasized by several authors.¹⁻² The outstanding symptoms that are common to both diseases are motor weakness or paralysis and varying degrees of tenderness and pain in the muscles of the back and extremities. The distribution of the involvement is an important point in differentiation, for in poliomyelitis the typical weakness is segmental and asymmetrical in distribution, whereas in polyneuritis the extremities are usually symmetrically weakened, the most severe involvement occurring proximally. Minor sensory changes can usually be detected in cases of polyneuritis and the cerebrospinal-fluid findings with albuminocytologic dissociation are characteristic of this disease. The prognosis in poliomyelitis in the acute stage is uncertain, residual paralyses being frequent, whereas in polyneuritis residual palsies are rare. The progression of paralysis is also different in these diseases, for in poliomyelitis the weakness is maximal during the acute phase, whereas in polyneuritis there may be a gradual increase in the degree of involvement and a spread to new muscles late in the course of the disease. Further details of the clinical picture and pathologic lesions have been discussed in recent reviews.³⁻⁸

In view of the similarity of symptoms in these diseases, we have treated patients with polyneuritis with hot packs and have observed as effective relief of muscle pain and tenderness as we have in poliomyelitis. To elucidate further the similarities in the behavior of muscles, we have studied by electro-

myography the patterns of electrical activity in the affected muscles of a series of patients with polyneuritis. Comparisons have been made with similar recordings from muscles in poliomyelitis in an attempt to throw light on the problem of muscle spasm and other dysfunctions in these diseases. In some cases comparisons have also been made with the recordings from cases with traumatic lesions of peripheral nerve, since these give direct evidence of the electrical behavior of muscle during regenerative changes in nerve.

METHODS OF STUDY

Ten cases of infectious polyneuritis from the Neurological Service of the Massachusetts General Hospital have been studied during the acute and convalescent stages of the disease. These had the characteristic symptomatology already described, including albuminocytologic dissociation in the cerebrospinal fluid.

The affected muscles were examined for clinical evidence of tenderness or pain on stretching, and their functional strength was assessed by the usual manual tests. The electrical discharges from these muscles at rest and during active and passive motion were recorded by means of an ink-writing oscillograph. Surface electrodes were usually employed, but in some cases these were supplemented by coaxial needle electrodes inserted in the belly of the muscle. The details of the technic have been fully described.⁹ Comparisons have been made with similar studies on 10 patients with poliomyelitis and on others with traumatic nerve lesions.

RESULTS

Resting Muscles

The first series of electromyograms were recorded from resting muscles in positions of complete relaxation. No electrical discharges are recordable from normal controls by this technic under such conditions.^{10, 11} In patients with polyneuritis, although the muscles were tender to pressure and stretching, spontaneous discharges were found only in the pres-

*From the Department of Psychiatry, the Department of Physical Therapy and the Department of Neurology, Massachusetts General Hospital. Aided by a grant from the National Foundation for Infantile Paralysis, Incorporated.

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¶Assistant in neurology, Harvard Medical School (on leave of absence).
§Also known as infectious neuritis, infectious polyneuritis with facic diplegia, Guillain-Barré's syndrome and Landry's paralysis.

from destruction of the anterior-horn cells cannot, of course, be influenced by any treatment applied

erative process, since the electrical patterns are indistinguishable and these discharges are correlated

PASSIVE PLANTAR FLEXION

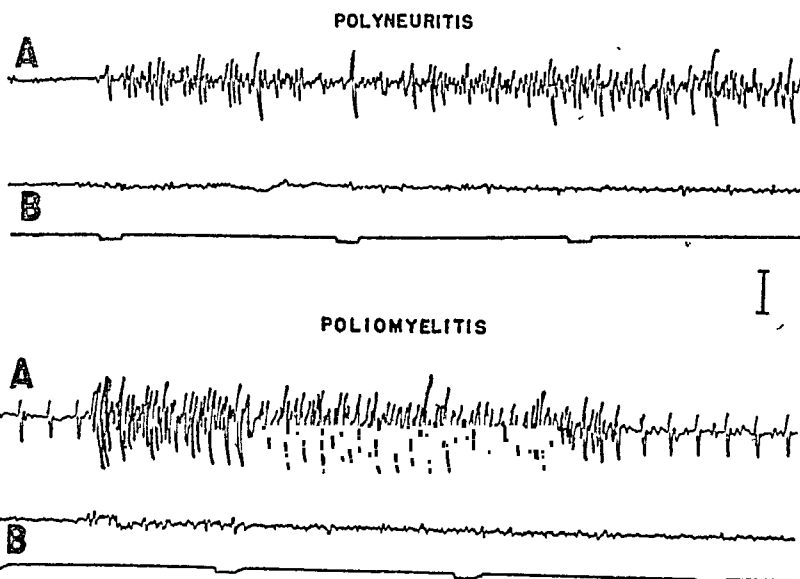


FIGURE 4. *Hyperirritability Elicited by Passively Stretching a Partially Paralyzed Muscle. The A tracings are from the anterior tibialis muscle, and the B tracings from the gastrocnemius.*

to the muscles, although the function of remaining motor units can be brought to the maximum by physical therapy.

It has been suggested that spontaneous discharges

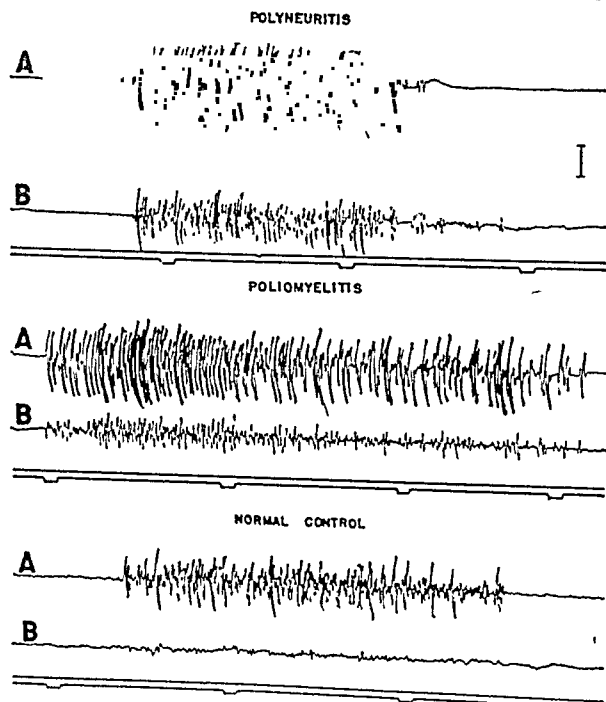


FIGURE 5. *Simultaneous Activation of Opposing Muscles on Voluntary Dorsiflexion.*

The A tracings are from the anterior tibialis muscle, and the B tracings from the gastrocnemius. Simultaneous activation occurs in polyneuritis and poliomyelitis, but not in a normal control.

from resting muscles in polyneuritis, poliomyelitis and traumatic nerve lesions are a sign of a regen-

with improving motor power. The histologic features of regenerating axons after traumatic nerve lesions are well known. The degenerative changes in peripheral nerves in polyneuritis have been described, and to account for recovery it is natural to assume that regeneration of axons takes place. In poliomyelitis no primary lesions in the peripheral nerves are generally recognized, although the virus may enter the cord by passage up an axon after experimental injection.²⁶ Axonal regeneration is, therefore, not thought to account for the improvement in motor strength that usually occurs. We have noted, however, that paretic muscles have diminished electrical excitability as measured by strength-duration curves, and that as power returns the excitability improves. This indicates that there are relatively severe although reversible lesions, presumably in the anterior-horn cells, and that secondary axonal changes may also occur. The electrical discharges probably represent returning function in motor units, but, of course, reveal no evidence of the types of histologic change that are taking place. The microscopical appearance of the axons is probably quite different in all three conditions under discussion, so that the term "regeneration" when used to describe our observations implies only a recovery process.

The simultaneous activation of opposing muscles observed in polyneuritis and poliomyelitis might be thought of as a type of "inco-ordination," as described by Kenny.^{13, 14} This is not, of course, inco-ordination in its usual meaning of abnormal muscular control in cerebellar disease. We prefer to interpret it as disruption of reciprocal innervation. In some

cases this disorder is apparently related to pain, the antagonistic muscle involuntarily contracting to prevent excessive movement. In poliomyelitis and in regenerating peripheral nerves after injury, we observed synchrony of action potentials, indicating severer disorganization of reciprocal innervation. In traumatic nerve lesions this probably represents abnormal axonal regeneration. There may also be similar abnormalities in the regenerative processes in poliomyelitis, although histologic evidence of this is lacking.

SUMMARY AND CONCLUSIONS

Electromyographic studies revealed the following similarities of muscle dysfunction in infectious polyneuritis and poliomyelitis: muscle tenderness and paresis are characteristic of both diseases, and the electrical abnormalities in both cases are correlated with weakness rather than with sensitivity. partially paralyzed muscles on stretching show hyperirritability, which can be relieved by hot fomentations; even at rest, paretic muscles are hyperirritable, discharging electrical potentials characteristic of regenerating motor units, and reciprocal innervation is frequently disrupted in polyneuritis and poliomyelitis, with resulting simultaneous activation of opposing muscles — this abnormality is probably secondary to painful motion.

The disorganization of reciprocal innervation is not so severe in polyneuritis as in poliomyelitis, for the simultaneous activation of opposing muscles in the former disease is not characterized by synchrony of component discharges.

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GERIATRICS: THE MEDICAL CARE OF THE ELDERLY*

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THE whole subject of geriatrics is relatively new. It can be compared to pediatrics, which was a blossoming subject when I was in medical school, but has now come to full fruition. The situation of the elderly has changed a great deal, because whereas a few years ago the average age of death was in the forties, a child born in the year 1943 may be expected to live to at least sixty-four years of age. The interesting thing is that the advances of medicine and public health have been directed almost entirely toward the early age group — that is, the age in which there has been improvement in mortality and morbidity statistics.

The man of forty to sixty-five lives no longer than he did fifty years ago, and there is a certain amount of evidence that he is no healthier. In other words, the present program of preventive medicine is enabling a great many people to live to sixty-five years but is not promising them anything when they do. It seems only fair that if they are to live as long as this, life ought to be made happier and healthier for them than it now is. Old age has been what one might call tolerated by the medical profession and by the public in general. No one is enthusiastic about old age. Certainly elderly people themselves are not particularly enthusiastic about it. In general, society has taken a negative and an entirely defeatist attitude toward old age. When the elderly are dead, society decrees a costly funeral and flowers.

As long as this negative, defeatist attitude continues, nothing is going to happen. Of course, part of this situation has been due to the fact that many of those who were looking for the alleviation of old age were not doing it from a medical or scientific point of view. All the folklore, all the tales about those who were interested in the elixir of youth — Ponce de Leon, in trying to find the Fountain of Youth, Ulysses, Sinbad the Sailor — show that these people were interested in only one thing, the re-creation of their sexual capacities, and not in the health of old age. This attitude has, of course, damaged the whole movement of geriatrics, when men are interested only in sex rejuvenation, and women only in keeping their charm, and, it will be noted, not usually their fertility.

I have no intention of discussing the damaging diseases of older people, — by which term is meant all those older than fifty-five and certainly those older than sixty, — such as advanced cancer, apoplexy and degenerative heart disease, about

which at that stage nothing can be done. It may be said in passing that it is only by the study of the advanced stages of disease that one can gradually get back to a study of the origins of the disease, therefore, a certain amount of attention paid to cancer, even advanced cancer, apoplexy, degenerative heart disease or what not may bear fruit in the long-distant future. A few simple diseases, however, are particularly frequent in old age. Gallstones, for example, increase in frequency with advancing birthdays, and it is likely that if people lived to be one hundred and twenty they all would have gallstones. Certainly, autopsies performed on people of eighty or over show almost uniformly the presence of gallstones. This may have some effect on the present attitude toward the diet of older people, which is discussed below.

Another illustration of the diseases of old age is diverticulosis, which is increasingly frequent with advancing age. X-ray studies show that nearly all people over sixty have a few diverticula. This condition may lead to an inflammation of one of the diverticula — the clinical entity known as diverticulitis.

Inflammation of the intestines also seems to be on the increase in the elderly. Appendicitis is usually thought of as a disease of young people, and it is certainly extremely common in that age group, but it again becomes frequent after the age of sixty. Since gallstones occur in elderly people, it is often taken for granted that a stomachache is due to them or to diverticulitis, but a passing plea must be made for the consideration of appendicitis, which often takes the gangrenous form in people over sixty.

As the aging process, like the growing process, has been studied, it has been found that to keep the machine running, just the same as to keep the machine growing, there must be food and nourishment. Probably one of the greatest mistakes, by and large, has been to let the aged select their own diet, the latter depending on the condition of their teeth, whether they could chew it or not, depending perhaps on their pocketbooks and on the convenience of getting the food. It is certain that whereas in the family circle great attention is paid to the food for growing children, little attention is paid to the food for elderly people, even though they need it to continue their somewhat waning energies. To repeat, probably the most important thing in elderly people is the administration of the proper food in adequate quantity and quality. Here may be seen *par excellence* the necessity of giving vitamins.

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For many years, I was rather an off horse concerning many of the vitamins, and it has only been in the last few years, when vitamin concentrates have become available, that I have been able to convince myself of their value, particularly in people with a restricted diet, and particularly with the aged. On the subject of vitamins, the elements of the vitamin B complex are particularly indicated in older people, for two reasons. One is that the vitamin B complex — this refers to most of the factors in that complex — is easily used up in the human economy, in marked contrast to vitamins A, C and D, and has to be replaced frequently, one might say continuously. Furthermore, as a person gets older his carbohydrate intake is apt to be increased, and he needs certain components of the complex for catalysts of the carbohydrates to assist digestion.

In older people — perhaps because they are subject to two conditions, one of them gallstones and the other diverticulosis — it is the common experience that the administration of a high amount of fat and of roughage is often contraindicated. The difficulty with fats may have some relation to the existing gallstones, or it may have a simple relation to the fact that fats are much more difficult to digest than are any other food elements.

In connection with diverticulosis, it is usually evident that elderly persons do not take the high-roughage diet, which is so fashionable nowadays and which middle-aged women take with such enthusiasm. Such a diet often disturbs the digestion as people get to sixty and beyond, and it is usually advisable to restrict, at least moderately, the amount of roughage that goes into the diet.

I used to be one of those who objected strenuously to many of the digestive remedies that at one stage were so popular. As one studies elderly people, one appreciates that one of the things that does occur in them is the diminution in function or secretion throughout the body, and the same is true of the digestive tract. As one practices clinical medicine more and more, one changes one's ideas a little, and with the elderly I have entirely changed my ideas about the efficacy of some so-called "digestive assistants," foremost of which perhaps is the addition of hydrochloric acid to the diet. It is well recognized that as a person gets older he is apt to have less and less hydrochloric acid in his stomach and has more and more gas, and it can be shown clearly that if the reaction of the food and of the material in the stomach is changed, other changes are produced all the way down the intestinal tract. Hydrochloric acid is mentioned merely as one of the possible adjuncts to the therapy of older people, because it represents a principle of supplanting or supplementing the juices and functions that have been reduced.

At one time, I was scornful about the use of pepsin. I have found, however, that in the aged, as with hydrochloric acid, pepsin and even the pan-

creatic extract are often of real value. The same is true of the administration of bile, as bile salts or otherwise. These substances are not as a rule highly effective among younger people, but toward the age of sixty there is usually a deterioration in the secretions of the body or a reduction in their total amount.

It is certain that older people are much better off without the laxatives that have been given so widely in the past. They now seem to be reserved almost wholly for the elderly, the argument being, as always, "It doesn't make any particular difference." But it does make a difference, and the intestinal tract can be helped by the same procedures that are used in younger people and by the same attempts to do without laxatives. I am a great believer in mineral oil, but realize that since it absorbs vitamin A, the latter may have to be replaced. I am also a firm believer in colonic irrigation for elderly people, done about once a week.

Just as I have discussed the gastrointestinal system, one can take the other systems and go over them with the same point of view. There is one system that comes to the mind of everyone who deals with older people — namely, the endocrine glands.

Potassium iodide, which is so often given for arteriosclerosis in older people, is prescribed for them by most physicians simply because it seems to agree with them. As a matter of fact, iodine is an important part of the thyroid secretion, and the latter is stepped up by the addition of iodine to the thyroid nucleoprotein. Furthermore, many elderly people with deficient thyroid secretion are greatly invigorated by the judicial administration of thyroid.

The disturbances of the endocrine glands are not always the disturbances of diminution, because after sixty toxic goiter is seen, and sometimes it persists and creates a puzzle in diagnosis. It is not necessary, however, to do a metabolism test on every old man who has a rapid heart and is losing weight just because one such gentleman happened to have an exophthalmic goiter and was cured by a subtotal thyroidectomy.

By all odds, the most frequent disturbance in the thyroid gland is the diminution in the quantity or quality of the thyroid secretion. Glycosuria — not to be confused with true diabetes — is frequent in elderly people but often requires no treatment. Elderly men are naturally enthusiastic about the possibilities of testosterone. Some of them have been through the various operations for rejuvenation, including the substitution of goat glands, and have not been made particularly happy except, perhaps, psychologically at times. The modern endocrine hormones are decidedly potent, but they are to be used with a certain amount of discrimination, just as are the female hormones, which are so useful in the menopause and subsequently. These two sets of hormones are often helpful in the elderly, but not so much from the personal view of the man

who wants to be a Don Juan or the woman who wants to be a Venus as from that of the general condition and general health.

No thoughtful person who considers the subject of diseases of the prostate gland fails to realize that although much benefit has resulted from the surgical approach, the final solution will probably be the taking of a pill, either by mouth or by injection. When it is discovered how and why the prostate gland grows old, they will be given substances that will control the prostatic hypertrophy and render surgical treatment unnecessary. But this development is still in the realms of wishful thinking and of experiment.

The most frequent causes of death in the elderly are of course the degenerative diseases of the heart, blood vessels and kidneys, and this is the field in which one would like to make progress. It is true, however, that at the moment there is no method and no clue for lessening the mortality of these diseases.

Dr. Timothy Leary has made out an excellent case for the damaging effect of cholesterol in premature and devastating arteriosclerosis. He calls this effect atherosclerosis. There is a certain amount of evidence of one sort or another that supports this view. On the other hand, a good deal of the experimental work now being done is based on the influence of certain diets on rabbits and other animals. Rabbits are herbivorous creatures, whereas man will eat anything, including meat. Of course, when cholesterol, which is an animal fat, is added to the diet of a rabbit or indeed to other animals there may be some findings that are not easily transferred to man. There is no indication that Italians, who live on vegetable fats and oils in contrast to Anglo-Saxons, who live on the protein ones, grow old any more gracefully or have any fewer diseases than the rest of mankind.

As a matter of fact, it is too bad that the real answer cannot be found. It is fashionable to state that degeneration of the heart and blood vessels is due to the wear and tear of life. But if this matter is closely examined it will be found that certain people develop conditions or diseases the explanation of which is, "No, that isn't wear and tear; that is just rust."

Those who are interested in general hygiene tell us that it is a matter of this, that or the other thing. But when it comes right down to it, health seems to have a great deal to do with the care with which one picks one's ancestors. If this is done with discretion and they had normal cardiovascular systems, they are apt to transmit them to their descendants.

It is also necessary to assume as a part of the treatment of old age that there is something else to live for than negative security. It is perfectly true that the occupants of old men's or old women's homes live a long time, or at least live almost indefinitely, but they live rather as vegetables than as real human beings.

In order to pass one's old age gracefully, pleasantly and helpfully, one must have some sort of objective in life, and that objective should be a little bit more than outliving somebody else. As one observes older people, however, it is interesting to see that this is often the dominating factor in their lives. It may be a son-in-law who is particularly despised; or the attitude may be that of two brothers who checked off people as they died, hoping, distinguished as they were, to be the oldest twins ever graduated from Harvard College when they passed away.

I saw a gentleman of ninety one day when he was in high spirits. He was a physician and a member of the Old Vienna Club. He rubbed his hands gleefully and said, referring to a lifelong friend, a fellow member of the club, "He isn't going to last long."

I mention these things not to cause amusement, but because there is some value in the psychological treatment of older people. They must have some incentive to live or they will, at times, literally curl up and die.

In 1914 a ninety-five-year-old lady called her family together and said: "I am an old woman, and I am going to die. I have taken to my bed." She also announced that she would give her brooch to so-and-so and her cameo to so-and-so. About that time World War I started and she became quite interested in reading the papers. The family rather neglected the nice old lady upstairs. Since they usually read the paper downstairs first, she would go downstairs and get the paper, and she became quite interested in how the war was going. She lived along all four years of the war, and then came the Treaty of Versailles. She then said that she did not think that the war had really proved anything. So she went to bed, summoned all her relatives and again said, "Now, I am going to die." But they said: "You can't put that over on us. You said that four years ago." But this time there was no World War I; there was nothing for this woman to live for, and she did what most older people do. It took her three weeks to run down, — it usually takes that long when old people take to their beds, — and that time she did die.

What I am pleading for is that older people must be treated psychologically as well as physically. I am no psychologist or psychiatrist, but when I went into the practice of medicine in Boston there was in practically every house on Beacon Street a room upstairs in which some old person lived and was never allowed to leave. People put lace caps on them or did something or other, and they vegetated there until they died. But one does not see that any more. The older people are not standing for it, and this is the first step in the treatment of geriatrics. These older people are being got out. Although I do not approve of their picking up gigolos and going dancing, at the same time a certain amount of that sort of thing is to be recommended. The family and the physician must have a certain amount of interest in older

people. They must have attention. Just today, one of your distinguished members came up here and talked in such an undertone that my old ears could not hear him, so I naturally switched off my attention. The younger people must talk loud enough so that we older ones can hear what they have to say.

I can do no better in closing than to tell a story concerning Dr. Stephen Smith, who was the first health officer of New York City. Because he was a health officer, he thought he knew all the principles of health and of righteous living. He was one hundred years old, and some people wanted to give him a dinner. I thought that was a terrible outrage. Then I thought, well, after all, he is a hundred years old, and he won't live long; he may have a good time, so why don't they do it? It may kill him, but what of it? They gave him the dinner.

Because of my curiosity about these things, I went over and talked to Dr. Smith, because I wanted to

ask him about his ancestors. He had any number of ancestors on both sides of his family that had lived to be one hundred or one hundred and five. He didn't like my question very much. Then I saw his daughter, who had given up her whole life to looking out for this old man. She was a spinster of about seventy-five winters, and she was not particularly communicative. I said to her: "Now, when people live to be old, there is always some reason for it. They either don't smoke or do smoke; they either don't drink or do drink; and they either drink in the morning or in the evening, or something of that sort. What do you think about that?" But, she would not bite on that. Finally, I said to her, "What do you give your fine old father to eat?" There was a little smile that came over her face, and she said, "Well, I feed him mostly on milk, whiskey and flattery, and the last two seem to be the more important!"

264 Beacon Street

PURPURA ANNULARIS TELANGIECTODES*

Report of a Case

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CASE REPORT

PURPURA annularis telangiectodes, first described by Majocchi,^{1,2} in 1896, has appeared infrequently in the American literature. In 1915, MacKee³ published a comprehensive review of the subject, along with extensive observations of a case of his own. In 1929, Scholtz⁴ reported a case and reviewed 7 cases reported since MacKee's original review. In 1930 and 1936, Way^{5,6} published case reports with histologic descriptions. In 1933, Levin and Tolmach⁷ reported a case in which the main clinical pictures of the skin corresponded typically with the accepted pictures of purpura annularis telangiectodes, and in which an autopsy was performed. Unfortunately, the latter cannot be accepted unreservedly because no histologic study of the skin lesions was made, and the described clinical course and gross autopsy findings were those of bacterial endocarditis, in which event, purpuric lesions might be expected to occur. In 1942, Wise⁸ published a review of the clinical and histopathological features of purpura annularis telangiectodes with its differential diagnosis from progressive pigmentary dermatosis (Schamberg⁹). The following case report seems justified because the clinical and etiologic investigation was more extensive than in any previously reported case.

H. L. J., a 20-year-old unmarried woman, was first seen at the Hitchcock Clinic on March 26, 1942, complaining of skin lesions on the lower halves of the legs. For 5 or 6 months she had had oozing, pustular lesions on both ankles, and for 2 weeks she had noted maculopapular, circinate, symptomless lesions over the lower halves of the legs, accompanied by slight edema of the left ankle. On May 29, she was seen by a dermatological consultant, Dr. Arthur M. Greenwood, of Boston, who made the diagnosis of purpura annularis telangiectodes. She was next seen on July 9, at which time no essential change in the skin lesions was noted.

The parents and seven siblings were living and well, and the family history was not remarkable in any way. In her childhood the patient had had measles, mumps, whooping cough and chicken pox, without complications. There was no history of rheumatic fever or of operations, injuries, major illnesses or previous hospitalizations. She had graduated from high school 2 years previously and had been a telephone operator for 1 year. The menses had begun at the age of 12 and had always been regular.

Physical examination was not remarkable, except for the skin lesions. The cardiac impulse was detected 8 cm. to the left of the midline in the 5th intercostal space. The sounds and rhythm were normal. The height was 66 inches and the weight 145 pounds. The temperature was 98.6°F., the pulse 80, and the blood pressure 110/60. There were purpuric, circinate, ulcerating, scarring, pigmented lesions of the legs and ankles and slight edema of the left foot. Two blood Hinton and two blood Kahn tests were negative. The red-cell count was 4,350,000 and the hemoglobin 11.8 gm. (Klett method). The white-cell count was 5350, with 2 per cent eosinophils, 1 per cent stab neutrophils, 60 per cent segmented neutrophils, 32 per cent lymphocytes and 5 per cent monocytes. The hematocrit was 40 per cent. The sedimentation rate was 74 mm. in one hour, and at another time 55 mm. The bleeding time was 2 minutes and 40 seconds, and the clotting time was 3 minutes. The platelet count was 217,500. The prothrombin time was 32 seconds (normal, 30 seconds). The blood nonprotein nitrogen was 25 mg., the blood sugar 83 mg., the plasma chlorides 590 mg., the serum cholesterol

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102 mg., the serum calcium 9.3 mg., and the serum phosphorus 3.3 mg. per 100 cc. Agglutination tests with *Brucella* organisms were negative. The plasma ascorbic acid was 1.5 mg. per 100 cc. A second-strength, intradermal tuberculin (P. P. D.) test was negative. A tourniquet test was negative. A radiograph of the veins of the left leg was performed after the injection of Diodrast into a superficial vein on the dorsum of the left foot. This showed normal visualization of the draining veins up to the femoral and external iliac veins. A radiograph of the chest was normal. An electrocardiogram was normal.

A biopsy of skin of the left leg was performed, the specimen being taken from an area showing telangiectasia, hemorrhage, pigmentation and atrophy. At the time of the biopsy, aerobic and anaerobic cultures were taken from the subcutaneous tissue, and these were sterile. Cultures on Sabouraud's medium were also sterile. Portions of the tissue were fixed in 10 per cent formalin and in Zenker's and Bouin's fluids, and the following stains were made: hematoxylin and eosin, Weigert's elastic tissue, Ziehl-Neelsen's, Masson's trichrome, and Turnbull-blue stain for iron. Serial sections were studied. A few capillaries showed hyaline thickening without other changes; others showed hyalinization of the walls accompanied by the formation of hyaline thrombi that completely occluded the lumens. There were scattered red cells in the connective tissue around such vessels, and an occasional widely dilated capillary with a ruptured wall was seen. In other areas there were proliferative intimal thickenings nearly occluding the lumens and, occasional round areas were seen that appeared to be recanalized, previously thrombosed vessels. These were surrounded by small collections of lymphocytes with occasional plasma cells and eosinophils. The capillaries around the hair follicles and sweat glands were particularly involved. Most of the other capillaries involved were in the superficial layers of the dermis. In some sections there was marked atrophy of the epidermis, which consisted of only two or three layers of cells; the immediate underlying dermis was fibrotic and showed hyalinized and thrombosed capillaries with extravasated red cells. Many of the sweat glands showed atrophic and fibrotic changes. In some of the hemorrhagic areas there were small collections of brown, granular pigment around the blood vessels, and these took the iron stain. The small arteries and veins of the subcutaneous tissue adjacent to the dermis were free of thrombotic and inflammatory changes. The elastic-tissue stain showed an apparent decrease in the elastic fibers of the dermis.

No acid-fast bacilli were found in the sections stained by the Ziehl-Neelsen method. (The perinuclear vacuolization of the epidermis described by Way⁵ appears to have no significance, since it has been seen in numerous sections of stratified squamous epithelium, including apparently normal tissues.)

SUMMARY

A case of purpura annularis telangiectodes is reported.

Extensive laboratory tests gave essentially normal values with the following exceptions: the blood cholesterol was moderately low, and the sedimentation rate was markedly elevated.

Histologic study of the skin lesions revealed thromboses, inflammatory changes in and around small blood vessels, hemosiderin deposits and atrophy, all of which have been previously described.

This case furnishes no evidence that purpura annularis telangiectodes is a dermatologic manifestation of a cardiovascular disease.

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ADDITION. In the paper "Pathology, Clinical Manifestations and Treatment of Lesions of the Intervertebral Disks" by Dr. Albert Oppenheimer, which appeared in the January 27 issue of the *Journal*, the following sentence should have been added to the first footnote in column 1, "Awarded the first prize in the competition for the Pray and Burnham Awards offered by the Trustees of the New Hampshire Medical Society."

MEDICAL PROGRESS

BLOOD BANKS AND BLOOD TRANSFUSION (Concluded)*

JOSEPH F. ROSS, M.D.†

BOSTON

TRAUMATIC SHOCK, BURNS AND HYPOPROTEINEMIA

The importance of the plasma proteins in the treatment of shock, burns and hypoproteinemia has been reviewed recently by Janeway⁶⁴ in this series of articles, and will not be repeated here. It may be pointed out, however, that desiccated plasma and solutions of albumin were developed specifically for use by the armed services, and their greatest value lies in their stability at room temperature for prolonged periods of time and in their concentrated form, which allows shipment in a minimum amount of space. For civilian use it is more convenient and economical to preserve whole plasma in the frozen state, and such plasma is probably more suited for general use than are the desiccated or fractionated products. Liquid plasma stored at 4°C. or at room temperature maintains its effectiveness in restoring the osmotic pressure of the blood,⁶⁵ but loses several of its other properties and is therefore not so satisfactory as is the frozen product.

In the event that plasma is not available, transfusion of whole blood should not be withheld from burned or shocked patients merely because hemoconcentration exists. In such cases donor blood is relatively dilute in comparison with the recipient's blood, and transfusion tends to arrest the development of further hemoconcentration.⁶⁶

Transfusion of whole blood is indicated in patients in shock when hemorrhage has been severe, and in burned patients when hemolytic processes⁶⁷ or inhibition of bone-marrow function has led to a lowering of the hematocrit.⁶⁸

INFECTIONS AND INFECTIOUS DISEASE

Specific and nonspecific antibacterial and antitoxic substances may be transferred by transfusions of fresh blood or plasma and are frequently of considerable value in the treatment of infections and infectious diseases.⁶⁹ Attempts to increase the concentration of these immune substances in the transfused material have led to the use of convalescent serums, immunotransfusions and highly concentrated immune globulins prepared from convalescent human subjects or immunized animals. Convalescent serums and immune globulins have proved highly successful in the treatment of certain infections — for example, scarlet fever, measles, mumps and pneumococcal and influenzal infections.⁶⁵ Im-

munotransfusion has not been so generally successful, probably because of the fact that the concentration of antibodies developed in the donor as a result of vaccine injections are not so high as those already present in the recipient.⁷⁰ Lyons,⁷¹ however, reported that transfusions of blood from properly selected donors were of considerable value in the treatment of hemolytic streptococcus infections.

The role of transfused leukocytes in combating infection has not been established. Donor leukocytes may aid in combating disease,⁶⁹ although it is not possible to elevate significantly the recipient's white-cell count by transfusion. Transfusion is of little or no value in the treatment of agranulocytic angina.⁷² It is frequently indicated in acute and chronic infections to supply erythrocytes and plasma protein. Occasionally, the benefits derived from such supportive therapy are pronounced.

Although the immune globulin substances appear to be quite stable, complement, leukocytes and perhaps other important antibacterial substances rapidly degenerate in stored blood.^{44, 55, 69} Consequently, fresh blood should be used for maximum effectiveness in the treatment of infections.

PRECAUTIONS

The importance of establishing absolutely the compatibility of blood before transfusion cannot be overemphasized. An error in blood grouping or cross-matching may — and all too frequently does — result in a severe transfusion reaction and death. Tests of compatibility should be performed only by adequately trained persons, and the materials and technics used must be scrupulously controlled. Excellent and concise descriptions of blood-grouping technics, with practical considerations of necessary precautions and sources of error, are to be found in the manual by Schiff and Boyd⁷³ on blood-grouping technic, which should be readily available in every laboratory performing such tests.

In contrast to the universally employed procedure of establishing donor-recipient compatibility in respect to the A, B, AB and O groups, tests for the Rh factor are not widely used, and until recently were performed only in a few research laboratories. The importance of the Rh factor as an isoantigen has recently been discussed by Hooker⁷⁴ and Wiener,⁷⁵ and it is apparent that most intragroup hemolytic transfusion reactions are caused by transfusion of Rh+ blood into sensitized Rh- recipients.⁷⁶ Even though the Rh factor is a poor antigen, and only 15 per cent of the white population is Rh-, the hazards associated with transfusion of Rh-incompatible blood

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are so great that tests for the Rh factor and transfusion of Rh-compatible blood should be made a routine procedure for all transfusions. Certainly, transfusions should never be given to pregnant women or to recipients receiving repeated transfusions unless Rh compatibility has been established.

Unfortunately, *in vitro* cross-matching tests — even with Landsteiner's test-tube technic and with incubation and chilling of the serum-cell mixtures — do not always detect potentially sensitive Rh-recipients. The avoidance of Rh-incompatible reactions can be ensured only by making tests for the Rh factor in the cells of both donor and recipient, and by transfusing Rh- recipients with Rh-blood. Such determinations require the use of potent Rh-agglutinating serum, which is still difficult to procure. Rh-factor determinations, however, can usually be obtained in centrally located laboratories.*

The indiscriminate use of so-called "universal donors" is dangerous, since transfusion of Group O blood may produce severe hemolytic reactions.⁷⁷ Hesse⁷⁸ reports that, in 46 cases, transfusion of universal-donor blood caused 20 deaths. He recommends that universal-donor blood be used only in cases of extreme emergency, and then only if the agglutinating titer of the donor serum for the recipient's cells is not higher than 1:32. Neutralization of isoagglutinins with specific Group A and Group B antigens has been recommended by Witebsky, Klendshoj and Swanson⁷⁹ and appears to make even high-titer Group O blood safe for transfusion into members of other blood groups. The pooling of several lots of plasma so dilutes and neutralizes the isoagglutinins contained in any one plasma that pooled plasma may be given without the hazard of producing intravascular agglutination.⁸⁰

The rate at which blood may be transfused safely depends to a large extent on the functional integrity of the recipient's cardiovascular system. In normal persons as much as 650 cc. of blood has been given in three minutes without adverse reaction⁸¹; the rate of flow usually recommended is 40 to 60 drops per minute, or 250 cc. per hour.

Blood and plasma that have been refrigerated may be transfused safely without preliminary warming.⁸² Indeed, mistaken attempts at warming may actually produce hemolysis or protein denaturation. Frozen plasma should be thawed at a temperature of 37°C., and the time used for thawing should not exceed thirty minutes. Slower thawing or thawing at room temperature results in the formation of a heavy fibrin precipitate.

Stored blood or plasma should be filtered before being transfused, since small aggregates of fibrin are prone to develop in even the best preservatives, and the introduction of such thrombi into the venous system may produce a fatal reaction.⁸³ Most filters tend to become clogged with these fibrin aggregates,

*In the New England area, Rh-factor determinations and potent Rh-agglutinating serum may be obtained from the Blood Grouping Laboratory (Children's Hospital, 300 Longwood Avenue, Boston).

with the result that they are frequently discarded and the blood or plasma is given without filtration. This is highly dangerous, since if there is enough precipitate to clog a filter, it will certainly clog the arterioles or capillaries somewhere in the recipient's body. Although not ideal, the glass-bead filter recommended by the British Medical Research Council^{84, 85} has proved satisfactory at the Massachusetts Memorial Hospitals.

Every precaution must be taken to prevent the transmission of disease by transfusion. The mere performance of a serologic test for syphilis is not adequate, since highly infectious syphilis may exist before the reaction becomes positive and even before the primary lesion appears.⁸⁶⁻⁸⁸ Eichenlaub and Stolar⁸⁹ state that in 41 cases of transfusion syphilis serologic examinations would not have aided in detecting the disease in 18 of the infected donors. Serologic testing of donors must be complemented by careful physical examination and questioning to exclude the possibility of latent or seronegative syphilis.

In view of the long latency of malaria, it may be unwise to use persons with a past history of this disease as blood donors, even though examination of a blood smear fails to reveal the presence of parasites.

The epidemic of jaundice following yellow-fever inoculations in the United States Army has been traced to the presence of small amounts of pooled human serum in the vaccine,⁹⁰ and it appears that the jaundice-producing agent is a filterable virus.⁹¹ Similar attacks of jaundice have been produced by the transfusion of blood and of convalescent serum,^{92, 93} and are presumably caused by a similar agent. The implications of these findings in the selection of blood donors are not yet definite, since donors of some of the jaundice-producing bloods are apparently healthy and there is no way of determining that their blood is icterogenic.

TRANSFUSION REACTIONS

Hemolytic transfusion reactions are unfortunately much more frequent than is usually suspected, the average incidence being about .2 per 1000 transfusions, with a mortality of 1.4 deaths per 1000 transfusions.⁹⁴ These rates place the risk of blood transfusion in the same range as the risk of some major operations, a fact that is all too often neglected. Many physicians take elaborate precautions to safeguard against much less important hazards, but depend on a young intern or an inadequately trained technician to establish the compatibility of donor blood. Fortunately, transfusion of incompatible blood does not always result in serious complications,⁹⁵ but the usual course of events following such transfusions is intravascular agglutination and hemolysis, hemoglobinemia, hemoglobinuria, severe systemic symptoms, oliguria, anuria, uremia and death in at least half the cases.^{78, 94, 96}

The pathogenesis of the renal failure that is the usual cause of death in these accidents is still ob-

scure. Considerable doubt has been cast on the theory that anuria and uremia are produced by mechanical blockage of the renal tubules by hemoglobin casts precipitated in acid urine, and on the belief that such blockage can be prevented by keeping the urine alkaline.⁹⁷⁻⁹⁸ Careful studies of kidneys from cases of fatal transfusion reactions have failed to account for the anuria on the basis of renal tubular obstruction. The primary lesion in such kidneys is a marked degenerative change in the convoluted and collecting tubules.^{17, 99} Furthermore, large amounts of pure hemoglobin may be injected intravenously and excreted in acid urines without producing any decrease in renal function or any untoward reaction.^{99, 100} Finally, maintenance of an alkaline urine in several typical hemolytic transfusion reactions did not prevent death.⁹⁹

It appears probable that transfusion-reaction nephritis is produced by the action of some toxic or antigenic substance on the tubular epithelium rather than by mechanical blockage of the tubular lumens. The nature of this hypothetical toxin is suggested by the recent experiments of Bing,¹⁰⁰ who found that hemoglobin, methemoglobin and metmyoglobin could be excreted in either acid or alkaline urine without disturbance of renal function so long as the alkali reserve of the subject was normal. Production of acidosis by the intravenous injection of lactic acid or hydrochloric acid prior to the injection of methemoglobin produced typical transfusion-reaction nephritis, with anuria, uremia and death. Such findings suggest that fatal human reactions occur when methemoglobinuria develops in patients with markedly reduced alkali reserves, as in severe shock.

The extreme seriousness of hemolytic transfusion reactions and the fact that about half the patients developing anuria die make it absolutely essential that effective therapeutic measures be instituted immediately in any patient suspected of having such a reaction. In spite of the evidence that transfusion-reaction nephritis is not produced by mechanical blockage of renal tubules, abundant clinical and experimental evidence supports the practice of alkalinizing the urine in all suspected cases.^{96, 101} To be effective, alkalinization must be accomplished rapidly, and this usually necessitates parenteral administration of alkalinizing agents. Because of the ready availability of sodium citrate in sterile ampoules in hospitals where transfusions are given, several authors have recommended the slow intravenous injection of 100 to 200 cc. of a 2.5 or 3.0 per cent solution of the drug, which, it is stated, produces a neutral or alkaline urine within fifteen minutes.^{102, 103} More physiologic in action, safer and probably more effective in alkalinizing the urine are solutions of sodium lactate ($\frac{1}{2}$ molar) and sodium bicarbonate (4 to 6 per cent), which can be procured in sterile ampoules and which should be available for immediate use in any hospital where trans-

fusions are administered. The oral administration of adequate amounts of sodium bicarbonate or other alkalies¹⁰² produces an alkaline urine, but the length of time and the amounts required vary greatly in different persons. Numerous other therapeutic measures directed toward stimulating renal function and the secretion of urine have been advocated, but there is little evidence of their effectiveness.¹⁰⁴ Transfusion of fresh compatible blood as soon as possible after the hemolytic reaction has occurred does appear to be of some value, perhaps because of its effect in stimulating blood flow through the kidneys.¹⁰⁵

It is evident from the confusion concerning the pathogenesis of transfusion nephritis and from the nonspecific nature and frequent failures of the numerous recommended therapeutic measures that the treatment of hemolytic transfusion reactions is unsatisfactory. It is better to avoid the necessity for such treatment by ensuring the compatibility of donor blood than it is to attempt treatment once a reaction has occurred.

Febrile reactions to transfusion are fairly frequent, and as a rule can be explained by the presence of pyrogens or impurities in solutions or by improperly cleaned glassware or tubing. Such febrile reactions may be serious in recipients who are critically ill or extremely anemic, and must be carefully guarded against by observing a scrupulous technic.

Allergic and anaphylactic reactions occur in 1 or 2 per cent of transfusions.⁹⁵ They vary in severity from mild urticaria to severe anaphylactic shock. Usually such reactions are mild and can be controlled by the injection of 5 to 10 minims of a 1:1000 solution of adrenalin. This type of reaction can be decreased in frequency by using only fasting donors, and it is now a routine requirement in many blood banks that donors must abstain from food for four to six hours before venesection is performed.

* * *

Blood banks and improved methods for the preservation of erythrocytes have made transfusion of whole blood a simple, economical procedure and have extended tremendously the therapeutic usefulness of transfusions. Blood plasma, originally a byproduct of the blood bank, now has its own particular fields of usefulness, and can be stored almost indefinitely without loss of therapeutic efficacy. The next great advance in transfusion therapy will no doubt be the preparation and use of purified fractions of the plasma proteins, — albumin (already in use), fibrinogen, thrombin, complement, specific immune globulins, isoagglutinins, enzymes and hormones, — each filling a particular therapeutic need.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

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CASE 30071

PRESENTATION OF CASE

A forty-one-year-old housewife entered the hospital because of diarrhea.

The patient was in apparent good health until three and a half years before entry, when she developed numerous grossly bloody stools accompanied by crampy, low abdominal pain. Three years before admission she had an x-ray examination and was told that she had a "duodenal ulcer." On a Sippy diet and "injections" she had considerable relief for a period of two years. It is not known what the injections consisted of and whether there was an examination of the stools. Six months before admission she developed vague, distressing, abdominal discomfort just below the left costal margin. The pain was not severe and had no relation to meals. Four months before entry she had sudden, severe, prostrating, left subcostal pain and stayed in bed for seven weeks. Following this she was extremely weak; she was able to get up but stayed at home. She had intermittent attacks of subcostal, flank and lower costal pain on the left. About two weeks before admission she developed loose liquid stools alternating with normal stools. There was no blood, tarry material or recognizable food particles in the stools. On one occasion at that time she vomited foul-smelling material. She was taken to a community hospital where barium studies were performed. She had lost 50 pounds in four months. No additional information was available except that she had had a hysterectomy and appendectomy three years before entry.

Physical examination showed a well-developed, poorly nourished pale woman. There was a slight apical systolic murmur, but the heart and the lungs were not otherwise remarkable. The liver was palpable at the costal margin. In the left upper quadrant was a palpable, tender mass from which a tubular structure extended to the right upper quadrant. There was tenderness in the left subcapsular region.

The blood pressure was 116 systolic, 68 diastolic. The temperature was 98.6°F., the pulse 75, and the respirations 20.

*On leave of absence

Examination of the blood showed a white-cell count of 14,000, with 87 per cent neutrophils. The hemoglobin was 8.5 gm. per 100 cc. The blood protein was 4.4 gm. per 100 cc. The urine gave a + test for albumin. A gastric analysis showed free hydrochloric acid and was guaiac negative. The stools were guaiac positive. A blood Hinton test was negative.

A gastrointestinal series showed a rather large stomach. A wide fistulous tract, measuring 7 by 1.5 cm., led from the greater curvature of the stomach opposite the cardia to the splenic flexure of the colon (Fig. 1). Peristalsis of the stomach was active, and there was normal passage of barium

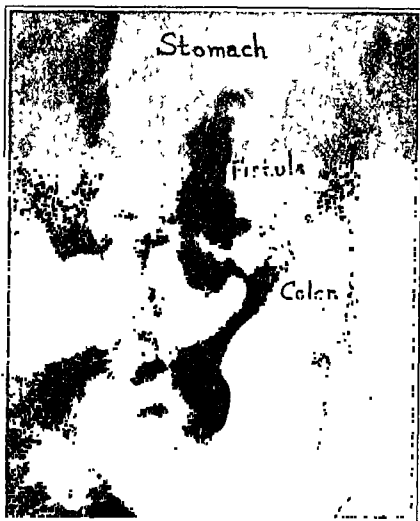


FIGURE 1. Roentgenogram following a Barium Meal.

through the pylorus filling a symmetrically non-tender duodenal cap. Six-hour films showed a small amount of barium still in the stomach, mixed with food material. The barium was scattered throughout the small bowel, but little seemed to have passed through the fistulous tract to the left colon. The colon was outlined with barium from rectum to cecum. The barium was mixed with fecal material, apparently following barium examination of the colon before admission.

On the tenth hospital day an exploratory laparotomy was performed.

DIFFERENTIAL DIAGNOSIS

DR. ROBERT R. LINTON: Before reading the x-ray report it is well to pause and see what one can make out of this history. First of all, it seems to me that

we are dealing with a woman who was in poor condition. For instance, she had a hemoglobin of 8.5 gm., which is half what it ought to be. She had a low serum protein, 4.4 gm. per 100 cc., whereas it ought to be in the neighborhood of 6 gm. She had a + test for albumin in the urine. These findings, I think, indicate that the woman was seriously ill, and had a condition that had probably been going on for some time. The first indication of anything wrong was three and a half years before she was admitted, and at that time she apparently passed grossly bloody stools accompanied by crampy, lower abdominal pain.

The passage of blood in the stools may be due to several things. First of all it may be due to hemorrhoids. If it was due to hemorrhoids, one would not expect it to be associated with lower abdominal pain. One should never stop at that diagnosis without investigating the colon further, both by sigmoidoscopy and barium enema, which was not done. Occasionally one sees grossly bloody stools from a duodenal ulcer. She did have a gastrointestinal series at that time, and a diagnosis of a duodenal ulcer was made. Whether she had that or not, I am not certain, but I am sure that that is not what she was suffering from when she came into the hospital.

The next thing of interest in the history is that six months before admission she developed vague, distressing, abdominal discomfort below the left costal margin. We have for the first time some evidence of the localization of the lesion. Four months before entry she had sudden, severe, prostrating, costal pain on the left, and later there was a mass noted in the left costal region. What conditions can give symptoms in this region with a presumable mass? The first one is pancreatitis, in view of the fact that some extension of the mass toward the right upper quadrant was noted, which is the general distribution of the pancreas. It seems to me that a patient with severe left subcostal pain could very well have a pancreatic lesion, not a hemorrhagic pancreatitis but some form of pancreatic cyst or low-grade pancreatitis. Again she may have had a lesion in the stomach, as the stomach lies in the left upper quadrant. It may have been a carcinoma of the stomach, with a subacute perforation into the left upper quadrant that had sealed off. Another condition is a lesion in the splenic flexure of the colon, such as diverticulitis or carcinoma. One cannot forget also that the kidney and the spleen are in the left upper quadrant, but we have no evidence that either of these organs was involved. Furthermore, in the laboratory studies it is important to notice that the patient showed free hydrochloric acid in the gastric analysis. There was no blood in the gastric analysis, but the stool did give a positive guaiac test. From that I conclude that she was not suffering from carcinoma of the stomach and that the blood in the stools was more likely coming from a lesion in the colon rather than from one in the stomach.

I am a little confused about the x-ray report. Perhaps it is correct as written, but I should like to ask Dr. Robbins whether the barium went from the stomach into the splenic flexure. Apparently it did not go from the splenic flexure into the stomach.

DR. ROBBINS: This is the point at which the barium, as I understand it, was said to go through from the stomach to the splenic flexure. I think there is definite evidence of rigidity of the wall of the stomach. This is the fistulous tract, and in this projection it shows best on the spot films. It is distorted and fairly long. There is a narrowed area in the distal transverse colon at the point where the fistula enters.

DR. LINTON: It is obvious from the x-ray films that she had a gastrocolic fistula, and I think that one can pick out several confirmatory items in the history. For instance, it is stated that two weeks before entry she developed liquid stools alternating with normal stools. That does not necessarily mean that she had a gastrocolic fistula but suggests it. On one occasion there was vomiting with foul-smelling material. These two things ought to make one think of gastrocolic fistula in a patient with a lesion in the upper abdomen. It is perfectly obvious from these x-ray films, which help us in diagnosing the lesion, that the condition was not one of pancreatic or duodenal origin.

I believe that there are three possibilities to be considered: carcinoma of the stomach with perforation and a fistulous tract into the colon; carcinoma of the colon with the reverse taking place; and a benign lesion, such as a diverticulum, that had formed an abscess and had perforated into the stomach. I think the last mentioned is the least likely in view of the fact that the patient showed evidence of chronic disease—the low hemoglobin and low serum protein. It is up to me to decide whether she primarily had carcinoma of the colon or of the stomach, which is a fairly hard decision to make. The fact that there was rigidity in the stomach wall makes me favor a primary lesion in the stomach rather than one in the colon. Furthermore, a lesion that had been going on as many years as this one had, if it involved the colon, would ordinarily have given obstructive signs, which apparently were not present. This lesion was in a silent area in the stomach and could have gone undiagnosed for some time. When she had the first gastrointestinal series, the lesion was probably overlooked, since it was in the fundus.

My final diagnosis is carcinoma of the stomach, with perforation and the formation of a fistulous tract between it and the colon.

DR. ROBBINS: The rigidity in the wall of the stomach could just as well have been produced by extension from a lesion elsewhere or by an inflammatory process. There is a definite narrow area of ulceration in the colon from which the fistula extends

DR. LINTON: Actually it makes little difference whether the lesion was in the stomach or in the colon, because both organs would have to be resected to relieve the patient. It is merely taking a long chance to see if one can guess the right one.

A PHYSICIAN: How do you explain the absence of occult blood in the stool?

DR. LINTON: I must admit that that is more indicative of a lesion in the colon than of one in the stomach. The free hydrochloric acid is also in favor of a colonic lesion rather than one in the stomach, but free acid does occur in carcinoma of the stomach, so one cannot draw any absolute conclusion.

DR. LELAND S. MCKITTRICK: Our reasoning was much like that of Dr. Linton. We were, however, more impressed by the radiologist's report than Dr. Linton was. We thought that the primary lesion was probably in the colon and that it had gone through into the stomach. We did not, however, feel strongly one way or the other.

We did a transverse colostomy and found an adherent mass in the left upper quadrant, which we did not thoroughly explore. We could not tell much about it but obtained the impression that it might be removable. About three weeks later she was re-operated on. During the interval she had seven or eight transfusions, but the hemoglobin at the end of that period was about 8.5 gm., practically what it was when she came into the hospital. At the second operation it was possible to take out the mass. We removed the greater part of the stomach, the spleen, about half the pancreas and the splenic flexure. Except for a thrombophlebitis involving the deep veins of the left leg, she made an uneventful convalescence.

CLINICAL DIAGNOSIS

Gastrocolic fistula.

DR. LINTON'S DIAGNOSIS

Carcinoma of stomach, with gastrocolic fistula.

ANATOMICAL DIAGNOSES

Adenocarcinoma of transverse colon, with extension into stomach.

Gastrocolic fistula.

PATHOLOGICAL DISCUSSION

DR. RONALD C. SNIIEN: As Dr. McKittrick has indicated, the resection included the greater portion of the stomach, the transverse colon, the spleen and a segment of the pancreas. The transverse colon and the stomach were intimately bound together. When the former was opened, an annular tumor about 4 cm. in length was found that had replaced the mucosa. Superiorly, in the center of the tumor, a fistula about 2 cm. in diameter led into the stomach on the greater curvature. From the gastric aspect the fistula was found to be situated in the center of

a mound produced by tumor infiltration of the stomach wall. The mucosa over this mound was ironed out but not destroyed, except at the portal of the fistula. To determine the origin of this tumor one must rely, in part, on the interpretation of the gross findings, and we believe that it arose in the transverse colon. Microscopically it proved to be a fairly well differentiated adenocarcinoma. The spleen was not involved, nor was the pancreas, although both organs were adherent to the mass.

CASE 30072

PRESENTATION OF CASE

A sixty-three-year-old woman was admitted to the hospital because of pain in the left leg.

The patient was in the hospital two years prior to admission because of a pathologic fracture through a benign giant-cell tumor of the left femur. The tumor was excised, leaving only the anterior medial and posterior walls of the cortex, which contained some of the original tumor. Grafts from the ilium were inserted. The patient was asymptomatic and moved around freely until two days before entry when she tripped over a rug and strained her leg, which necessitated the use of a cane. One month before admission she noted a mass in the left lower quadrant of the abdomen. There was no pain except for a "kink" on one occasion. She had no other symptoms.

She had been constipated for many years and had noted no change recently. Seven months prior to admission she noted a small amount of blood in the stools, but none since. A barium enema at that time was negative.

Physical examination showed a grapefruit-sized movable nontender mass in the left abdomen. It could not be moved into the pelvis or the flanks. There was anterior bowing and marked thickening of the left femur.

The blood pressure was 155 systolic, 75 diastolic. The temperature, pulse, and respirations were normal.

X-ray examination of the left femur showed progressive expansion in the involved area since the last examination. This was more marked in the lower portion, where numerous cyst-like cavities were seen that were divided by coarse trabeculae of bone. The bone grafts previously described were still in position and maintained their density. There was evidence of a fairly recent fracture of the anterior cortex at the upper extremity of the involved portion of the femur with anterior bowing, which was greater in degree than it was two years previously. There was no apparent soft-tissue mass in the left pelvis. A barium enema passed without delay from the rectum to the cecum. The proximal sigmoid was displaced laterally by a palpable mass

in the left side of the pelvis. The mass was extrinsic to the sigmoid and not grossly adherent to it. The rest of the colon was negative. A post-evacuation film showed contraction of the entire colon, with normal mucosal relief.

On the fifth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD B. BENEDICT: The first question that occurs to me is a rhetorical one. I might ask why an endoscopist was asked to discuss a bone tumor. The first answer is a flattering one — possibly they thought that I am a good diagnostician. The second is that they wanted to "take me for a ride"; the third, that they could not get anyone else.

DR. RONALD C. SNIFFEN: Let us assume that the first is correct.

DR. BENEDICT: Could the pathologist be mistaken about the pathological diagnosis of benign tumor? You do not have to answer that now, Dr. Sniffen, but you might think about it.

Perhaps we might first look at the x-ray films.

DR. LAURENCE L. ROBBINS: This is the bone lesion as it was originally seen. These films were taken in 1941. The location of the lesion is of interest. Apparently it is a trabeculated lesion with large cystic areas and appears to involve the entire bone, both the cortical and medullary portions. So far as I can see there is no evidence of break in the cortex other than what perhaps can be explained by a small fracture. I see no evidence of a soft-tissue mass. On this film, approximately three years post-operatively, you can see the changes that have taken place. The lesion has continued to expand, with loss of cortex in this area, but that does not necessarily mean that the lesion has become malignant. One wonders about it, however. There is soft-tissue swelling beyond a break in the cortex and evidence of fracture in the upper portion of the lesion, which probably explains the acute episode.

So far as the examination of the colon is concerned, the fluoroscopist definitely had the advantage, but I am inclined to think that the pressure is more on the transverse colon than on the sigmoid; that is, the transverse colon appears to be displaced in the distal portion. The sigmoid may have been displaced fluoroscopically.

DR. BENEDICT: The record states that it was displaced laterally by a palpable mass in the left side of the pelvis.

DR. ROBBINS: If there was a mass I should put it above the transverse colon.

DR. BENEDICT: Was there a chest plate?

DR. ROBBINS: Yes; it was negative.

DR. BENEDICT: There are several things against a benign giant-cell tumor. Geschickter* states that no giant-cell tumor has recurred after primary radi-

cal resection. Furthermore, giant-cell tumors usually occur in the end of the bone. Fractures are undoubtedly occur, but I wonder if one could expect two fractures in a recurrent giant-cell tumor. Such tumors occasionally become malignant, and I suppose that could have happened here.

What do you say, Dr. Sniffen, about the possibility of an erroneous microscopic diagnosis?

DR. SNIFFEN: In this case I should say "No."

DR. BENEDICT: Definitely?

DR. SNIFFEN: Yes.

DR. BENEDICT: By microscopic examination?

DR. SNIFFEN: Yes.

DR. BENEDICT: What do you think, Dr. Robbins? Is the bone tumor malignant by x-ray?

DR. ROBBINS: The sections were taken at the time of the original films, and we do know that some giant-cell tumors become malignant. I do not know whether this is malignant now.

DR. BENEDICT: I should like to relate the lesion to the abdominal mass, carrying out Dr. Richa Cabot's teaching of having one diagnosis to cover everything. In that case it would have to be malignant tumor in the abdomen with metastases to bone. I thought of an ovarian tumor, but it was described as not being in the pelvis, and ovarian tumors seldom metastasize to bone. Furthermore the plain film of the pelvis was said to have been negative. Tumors of the colon do go to bone, but not often. The barium enema was negative except for an extrinsic mass, which tends to rule out the colon.

The tumors that metastasize to bone common are those that originate in the prostate, breast, thyroid gland and kidney. I suppose that examination of the breast and thyroid gland was done and that a mass would have been noted. Tumors of the kidney frequently metastasize to bone, and the mass felt in the abdomen is consistent with a renal tumor. In addition, symptoms of the metastatic lesion rather than of the primary tumor may appear first. There is no record of x-ray films of the kidneys. The urine is not reported, and there was no pyelogram. Is there anything in the record about these?

DR. SNIFFEN: The only finding recorded of remote significance is a rare red cell and rare white cell in the urine.

DR. ROBBINS: I think that I can see the left kidney; it appears to be normal.

DR. BENEDICT: Tumors of the lung and occasionally those of the stomach and esophagus go to bone, but we have no evidence of anything in the chest, stomach or esophagus. Lymphoma occasionally goes to bone, but usually to the vertebrae and this is not the x-ray picture of a lymphoma. Pathologic fractures are uncommon in lymphoma of the bone, and there should have been other evidences of lymphoma. From the x-ray standpoint this is apparently not an osteogenic sarcoma, because there is new-bone formation at the epiphyses.

*Geschickter, C. F., and Copeland, M. M. *Tumors of Bone*. 709 pp. Philadelphia: Lancaster Press, 1931. P. 325.

end. Furthermore, the patient is usually somewhat younger and pathologic fractures frequently occur. I was going to put all my money on a hypernephroma with metastases to the femur, but Dr. Robbins and Dr. Sniffen believe that this is not a malignant bone tumor, and Dr. Robbins says that the left kidney outline is normal so far as he can tell. I do not know of any way to explain these two conditions on the basis of a benign giant-cell tumor except by making two diagnoses, and even then I cannot name a tumor of the left lower quadrant that is not in the pelvis, not in the flank and not in the colon. In spite of all the arguments against a malignant bone tumor I am going to say that this was a hypernephroma with metastasis to the femur.

DR. BENEDICT'S DIAGNOSIS

Hypernephroma, with metastasis to femur.

ANATOMICAL DIAGNOSIS

Malignant lymphoma, lymphoblastic type, of stomach, with extension to transverse colon and involvement of regional lymph nodes.

PATHOLOGICAL DISCUSSION

DR. SNIFFEN: Dr. A. W. Allen operated on this patient, and I am sorry he is not here to discuss the case. I shall read a portion of his operative findings.

The abdominal mass just below and to the left of the umbilicus was found to be a massive cancer in the region of the midtransverse colon. There were implants in the



FIGURE 1. Photograph of Stomach.

DR. FLETCHER H. COLBY: Would you expect a renal tumor to displace the colon the way this did?

DR. ROBBINS: No; but I cannot be sure about the displacement of the colon. The fluoroscopist said one thing, but what I see on the films is transverse colon that may be displaced by a renal tumor. There is one peculiar thing — the gas shadow above the transverse colon appears to be in the mass displacing the colon; if one considers both films together, the gas shadow could be due to something in the stomach.

CLINICAL DIAGNOSES

Ovarian cyst.

Carcinoma of stomach.

great omentum and in the gastrocolic ligament. Further exploration revealed that the source of the tumor lay in the stomach itself. There were nodes along the left gastric vessels, and nodes posteriorly to the celiac axis. The liver, however, was entirely free of disease; moreover there were no free peritoneal implants. After evaluation of the entire situation we decided that the tumor was resectable.

A total gastrectomy, a transverse colectomy and a splenectomy were performed.

I do not see how Dr. Benedict could possibly have made the diagnosis. I am afraid that he was the victim to illustrate an interesting gastric lesion. The two lesions were not related; the bone lesion was a benign giant-cell tumor.

The resected specimen was one of stomach, transverse colon and spleen. In the stomach there were two major masses, one on the greater curvature,

about 10 cm. in diameter, and the other on the lesser curvature, about 7 cm. in diameter (Fig. 1). These were separated by several centimeters. In the rest of the mucosa there were several smaller nodules, and the rugae in general were large and moderately firm. Both masses invaded all coats of the stomach and had reached the serosa. The larger mass had invaded the transverse colon, which contained a small submucosal nodule. The mucosa over the tumors was atrophic, but apart from an area of central ulceration over the larger mass, it was intact. These lesions microscopically proved to be lymphoma of the lymphoblastic type.

It might be well to stress the fact that when one finds this picture — multiple tumors that originate in the stomach wall, protrude into the lumen and iron out the mucosa, with a central area of ulceration — one should seriously entertain the diagnosis of lymphoma. This also holds for the connective tissue tumors, such as leiomyosarcoma and fibrosarcoma. Some of the regional lymph nodes were free from lymphomatous change, and some were involved. In an early lymphoma of the stomach one does not expect the lymph nodes to be involved, but in an advanced tumor such as this, it is more likely. The spleen was normal.

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REHABILITATION AND RE-EMPLOYMENT

THE number of men rejected by the armed forces or honorably discharged with a "certificate of disability" is already great and will, of necessity, increase to an extent that may make it a difficult task for the civil community to absorb them adequately and gainfully. The proper rehabilitation and re-employment of these men is of the utmost importance if we are to avoid the tragic aftermath of the last war, and much of the responsibility for any future program rests on the civilian physician — for to him the discharged soldier will and should turn for help, guidance and assurance.

It is well to remember that the primary if not the sole objective of the induction stations of the armed

forces is to procure a sufficient number of men who are physically fit for the rigors of general military service. The rejection of a selectee does not imply that he is incapable of living a normal existence or of being a useful civilian in his community, as he may well have been in the past. In a similar way, men are discharged from the armed forces with a "certificate of disability" because, for one reason or another, they are no longer able to stand the extreme stress and strain of modern warfare. Again there is no necessary implication that these men cannot return to a useful civilian life; they have been discharged solely because they are not fit for combat duty. It has not, however, been sufficiently stressed or publicized that many men are rejected or discharged for defects entirely compatible with normal civilian life. The man who has been rejected by an induction station or discharged from the armed forces may have a previously undiscovered disease that can and should be treated by his own physician. On the other hand, it must be emphasized that chronic diseases, either mental or physical, that have previously been known should gain no new significance or importance when the soldier returns to his home. The mere fact that he has been rejected or discharged must neither be a stigma against the man nor a cause of special anxiety to his family and friends, though all too frequently it is. The high-strung, tense person with frequent gastric complaints without organic basis presents no new problem when he returns home with the diagnosis "psychoneurosis, anxiety type." If he was an acceptable and useful member of society before, there is no reason why he should not continue to be such, provided his problem is understood and he himself is helped.

A man may have been gainfully employed for a period of years and yet be rejected by the armed forces for some psychiatric trait that makes him inefficient as a soldier; this fact renders him no less efficient as a civilian employee. Personality disorders that might well disqualify a man or cause his subsequent discharge again acquire no new significance. What may upset the family and may prejudice a future employer is that traits which had in civil life been regarded as erratic conduct or personal peculiarities were considered by the medical officers to be disqualifying for combat service. A man may be rejected for "healed tuberculosis," yet this diagnosis may thoughtlessly be translated into

about 10 cm. in diameter, and the other on the lesser curvature, about 7 cm. in diameter (Fig. 1). These were separated by several centimeters. In the rest of the mucosa there were several smaller nodules, and the rugae in general were large and moderately firm. Both masses invaded all coats of the stomach and had reached the serosa. The larger mass had invaded the transverse colon, which contained a small submucosal nodule. The mucosa over the tumors was atrophic, but apart from an area of central ulceration over the larger mass, it was intact. These lesions microscopically proved to be lymphoma of the lymphoblastic type.

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MEDICAL EPONYM

SCHMORL'S DISEASE

Dr. Christian Georg Schmorl (1861-1932), discussed "Ueber Dehnungs- und Zerreißungsvorgänge an den Bandscheiben und ihre Folgen. [Events Preceding Expansion and Rupture in the Menisci and their Results]" at the twenty-second session of the Deutsche Pathologische Gesellschaft in Danzig, June 8 to 10, 1927. A report of his presentation may be found in the *Centralblatt für allgemeine Pathologie und pathologische Anatomie* (40:244-246, 1927). A portion of the translation follows:

The normal turgor of the menisci may thereby so injure the spongiosa of the vertebral bodies as to lead to an abnormally marked indentation of the menisci. This is particularly the case if the spongiosa has deteriorated as the result of disease of the bone substance or the marrow, and its weight-bearing capacity damaged. . . .

Under normal conditions also an injury to the spongiosa may result from the pressure due to turgor. This injury may be especially observed in young persons in whom endochondral growth is in process of conclusion or indeed has ceased. The injury is here limited to the region of the nucleus and is most probably to be attributed to a deterioration of the cartilage plates. . . .

As a result of the indentation of the menisci there takes place an extension and thinning of the cartilage plates. Finally, excessive expansion, characterized by the formation of delicate fissures and rupture, occurs, usually in the nuclear region on both surfaces of one and the same meniscus at symmetrically located points. . . .

... cavities of greater or lesser size arise in the spongiosa. . . .

Cartilaginous nodules appear, which frequently lie at symmetrically situated points of the two surfaces of the menisci.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

COUES — William P. Coues, M.D., of Brookline, died January 13. He was in his seventy-second year.

Dr. Coues received his degree from Harvard Medical School in 1894. He was appointed senior intern in surgery at the Massachusetts General Hospital in 1894. He was a member of the Massachusetts Medical Society and the American Medical Association.

CRONIN — Edward J. Cronin, M.D., of Brighton, died February 11. He was in his forty-seventh year.

Dr. Cronin received his degree from Tufts College Medical School in 1921. He interned at St. Elizabeth's Hospital and was staff secretary there at the time of his death. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, five children, three sisters and five brothers survive.

EMERSON — Francis P. Emerson, M.D., formerly of Boston, died at the home of his daughter in Franklin on January 19. He was in his eighty-second year.

Dr. Emerson received his degree from Columbia University College of Physicians and Surgeons in New York, in 1886. He was formerly professor of Otorhinolaryngology and Ear, Nose and Throat at the New York College of Medicine. At one time he was a member of the staffs of the Brooks Hospital and the Massachusetts Women's Hospital. He was a member of the Massachusetts Medical Society, the American Medical Association, the American Association for the Advancement of Science, the American Otological Society, the American Laryngological Society and the New England Laryngological and Otological Society.

One daughter survives.

KITE — Walter C. Kite, M.D., of Milton, died February 5. He was in his eightieth year.

Dr. Kite received his degree from the University of Pennsylvania School of Medicine, Philadelphia, in 1893. He served internships in hospitals in Philadelphia, Atlantic City and Wilkes-Barre, Pennsylvania. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, a son, a daughter, a grandson and a brother survive.

RICHARDSON — EDWARD P. RICHARDSON, M.D., of Brookline, died January 26. He was in his sixty-third year.

Dr. Richardson received his degree from Harvard Medical School in 1902 and for sixteen months before graduating was surgical house officer at the Massachusetts General Hospital. As a specialist in surgery he was at various times, assistant visiting surgeon to the Massachusetts General Hospital, and consulting surgeon to hospitals in Gardner, Milford, Brockton, Attleboro and Plymouth. In 1915, he served with the First Harvard Medical Unit at British General Hospital No. 22, near Etaples, France, as a temporary honorary major. In July, 1918, he was commissioned a captain in the United States Army Medical Corps. He was then assigned to Evacuation Hospital No. 30 and promoted to major in September and arrived in France with his unit on Armistice Day. In 1925, he accepted a full-time position at the Massachusetts General Hospital as chief of the West Surgical Service and associate professor of surgery at Harvard Medical School, later becoming John Homans Professor of Surgery. He held these positions until 1931, when he was obliged to withdraw from active practice because of ill health.

He was a member of the Massachusetts Medical Society, American Medical Association, American College of Surgeons, American Surgical Association, Southern Surgical Association, and Society of Clinical Surgery.

Three sons survive.

RILEY — Charles A. Riley, M.D., of Newton, died January 30. He was in his sixty-third year.

Dr. Riley received his degree from the Jefferson Medical College of Philadelphia in 1905. He was a member of the staff of the Brooks Hospital and a consultant for the public-health services in Boston and Newton. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, a son and a daughter survive.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

HYLAN — N. Wicker Hylan, M.D., a major serving as flight surgeon with the Air Corps of the Army of the United States in England, was killed on January 28 as the result of an aircraft accident. He was in his thirty-seventh year.

Dr. Hylan received his degree from Tufts College Medical School in 1935. He formerly practiced in Derry and went overseas in June, 1943. He was a member of the New Hampshire Medical Society.

His widow, four children, a sister and two brothers survive.

WAR ACTIVITIES

INDUSTRIAL MEDICINE

PRECAUTIONS FOR THE HANDLING OF CHLORINATED COMPOUNDS

The Halowax Products Division of the Union Carbide and Carbon Corporation has recently circularized to all its customers, and to health agencies, a pamphlet, "Precautions for Handling Chlorinated Hydrocarbons." Chlorodiphenyl and Related Compounds. His action has been made necessary because of the frequency with which workers have developed acne after continuous exposure to these materials in the manufacture of synthetic waxes. The statement describes specific preventive measures, including engineering control procedures, selection of workers, health supervision of workers and personal-hygiene practices.

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THE USE OF REFRIGERATION IN AMPUTATIONS AND PERIPHERAL VASCULAR DISEASE*

E. EVERETT O'NEIL, M.D.†

BOSTON

DURING the last three and a half years, an attempt has been made at the Boston City Hospital to evaluate the role of reduced temperatures in the treatment of various types of peripheral vascular disease. Particular interest has been directed toward the employment of refrigeration as an anesthetic agent in amputations of the extremities for gangrene due to primary arterial disease. In addition, the effects of localized chilling of tissues in states of impending ischemia, due to sudden arterial occlusion, sepsis and venous thrombosis, have been observed.

The use of cold as a therapeutic agent is not new. Ice applications and cold compresses for the relief of pain and reduction of inflammation are as old as medicine. Within recent years, newer concepts of refrigeration have been developed. The familiar work of Fay and his associates in reducing temperatures over long periods of time in patients suffering from cancer emphasized that a lowered metabolic state, comparable to hibernation in lower animals, is possible in human beings. Whatever the value of these studies so far as any positive attack on the broad field of malignancy is concerned, they pointedly demonstrate that tissue metabolism can be slowed to a degree hitherto not thought possible. A more recent development, and the one that this paper is particularly concerned in describing, has been prompted by the observations of Allen¹ on the use of refrigeration in diabetic or arteriosclerotic gangrene or both.

Experimental Evidence

There is ample evidence that when the extremities of animals become totally ischemic as the result of the deprivation of blood supply by a tourniquet, exposure to room temperature or to an increased temperature results in rapidly progressive

tissue necrosis. It has further been observed that the reduction of temperature enables limbs to survive for a much longer period of time. Brooks and Duncan,² for example, noted that a rat's tail became gangrenous within four hours after ligation at a temperature of 40°C. When, however, the temperature was reduced to approximately 4°C., the survival period was extended to as long as four days. Allen³ observed that the hind legs of rabbits, cats and dogs survive asphyxia for thirteen to fifteen hours at room temperature. When the temperature is reduced and maintained at approximately 2 to 4°C., the dangers of ligation are greatly diminished. Under these conditions, limbs showed a survival period of fifty hours or longer. Furthermore, the phenomena of shock, thrombosis, infection and injury to blood vessels and nerves were markedly inhibited.

Clinical Considerations

The results of animal experimentation obviously suggest imitation in human beings. It thus appears that the use of ice as an anesthetic agent might be of particular value in a group of poor-risk patients, in whom mortality in major amputations has always been appallingly high. The type of patient found in the clinics of municipal institutions—undernourished, neglected, discouraged, often with an advanced state of peripheral arterial insufficiency, seen for the first time with rapidly spreading gangrene and sepsis, and with histories of previous cardiac and cerebral accidents—immediately suggests the likeliest candidates for this form of therapy. In these patients, spinal or general anesthesia, with additional operative shock, are all too frequently the factors militating against recovery. On the other hand, it is probable that, except in rare cases, the method of refrigeration has little to offer in groups of selected patients watched carefully by organized groups of physicians and surgeons. In these cases, anesthesia probably seldom contributes to mortality.

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 26, 1943.

†Visiting surgeon, Boston City Hospital, clinical professor of surgery, Boston University School of Medicine

Tourniquet and Refrigeration

The method under discussion, as has been stated above, is essentially one of combined ligation by means of the tourniquet and refrigeration. The application of the tourniquet itself is of considerable importance. Rubber tubing, 10 to 12 mm. in diameter, is the best material for ligation. Allen¹ has demonstrated that wide bands, such as an Esmarch bandage, by traumatizing wide masses of tissue, contribute to a greater degree of secondary shock than do narrow bands. Two turns of the tourniquet are made at the selected site, and the tubing is held in place by a clamp or knot, care being taken that the skin is not pinched. The tourniquet is applied as tightly as possible. As a preliminary measure,

thermometer, held against the skin from time to time, will enable the leg to be kept at the proper temperature level.

In the average case, in our experience, it takes between two and two and a half hours to produce sufficient anesthesia to allow a painless amputation. In a thin, emaciated, arteriosclerotic limb, anesthesia is necessarily attained more quickly than in the extremity of a young, muscular patient who requires an amputation because of trauma.

No attempt should be made to hasten a refrigeration amputation for fear of too long constriction of the limb by a tourniquet. In several of our cases the tourniquet has remained on for ten to twelve hours, and in no case has there been any interference with



FIGURE 1. Leg from Tourniquet to Toes Encased in Cracked Ice and Surrounded by Rubber Sheeting.

The lower leg and foot are exposed for demonstration purposes.

several ice bags are placed at the ligation level for a few minutes, in order to minimize any discomfort incidental to the placing of the rubber tubing. Refrigeration is immediately begun.

In the case of a low thigh amputation (Fig. 1), the entire leg and thigh up to the tourniquet site are surrounded by cracked ice encased in rubber sheeting or in a special container* built for the purpose (Fig. 2). A skin temperature maintained at about 8 to 10°C. has been found most desirable, assuring that the part is chilled and not frozen (Fig. 3). It must be emphasized that refrigeration is not freezing, and the terms should not be confused. Tests by an ordinary house or laboratory

subsequent primary wound healing of the stump. The usual criticism of undue trauma to blood vessels from a tourniquet does not appear to be warranted under conditions of refrigeration. Moreover, in certain cases we have intentionally waited longer than the customary anesthesia period in order that the patient's general condition might improve. It has been apparent that reduced temperatures have definitely promoted the comfort of the patient.

As a rule, little if any preliminary medication is needed, unless the patient is apprehensive or nervous. Indeed, the improvement of the mental and physical state after refrigeration has been initiated is dramatic.

Operation and Aftercare

When the desired anesthesia has been reached, the patient is moved, with the ice container, to the

*This container was designed by Dr. Andrew Webster, intern on the Third Surgical Service, Boston City Hospital, who has assisted in this study. The Therm-O-Rite Products Company, Buffalo, New York, has developed an electrically operated, thermostatically controlled refrigeration unit that does away with the obvious difficulties associated with ordinary refrigeration methods.

operating room and placed on the table. The container is removed and the limb is prepared for operation. The incision is made 10 to 15 cm. below the level of the tourniquet (Fig. 4). The type of amputation should be the simplest. Our preference is for a circular amputation, with staggering of skin, muscle and bone layers and without the formation of flaps, leaving the skin incision dog eared on each side. This method assures a comfortable and ultimately a good-looking stump. No drains are ever used (Fig. 5). The omission of drainage is as essential to primary healing in the refrigerated stump as it is in elective amputations done under any of the commoner methods of anesthesia.

It is our conviction that the guillotine amputation with no attempt at closure is preferable to the em-

limb at a lower limit than ever before thought practical — for example, 5 to 7 cm. above the ankle. Since the saving of life and not the correct fitting of a prosthetic appliance is the purpose in many older patients, this procedure is a reasonable one. It is recommended in selected cases.

Patients undergo refrigeration amputations without pain and without shock. Pulse and blood-pressure levels are not changed by the operative procedure. The usual postoperative discomforts — nausea, vomiting, and pain — are not experienced. The following case reports illustrate these facts.

CASE REPORTS

CASE 1. S. G., a 10-year-old boy, suffered a compound fracture of both bones of the left forearm on October 4, 1941, when he fell while playing in a stable. He was operated on shortly after admission to the hospital. The usual procedure

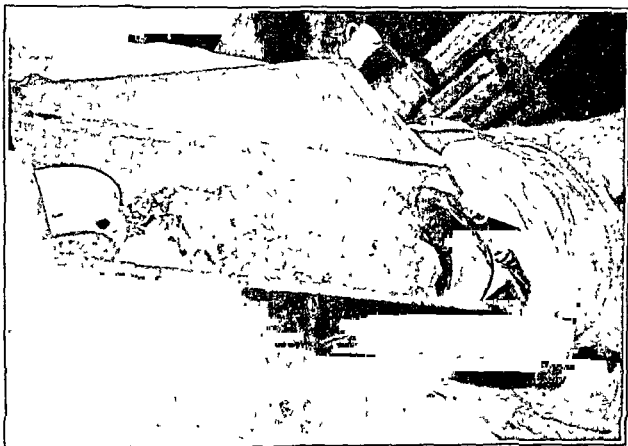


FIGURE 2. Home-Made Wooden Container.
This box is much easier to handle than rubber sheeting.

ployment of drains and that in the presence of rapidly ascending infection it is the procedure of election. The tourniquet is released just prior to closure of the wound. Circulation returns promptly, and there is bleeding in proportion to the vascular supply of the limb. It will be observed that there is no thrombosis within the blood vessels and that the blood is in its normal fluid state. The muscle bundles appear healthy and a somewhat brighter red than usual, comparable to the color of meat subjected to icebox temperature.

In this series of cases, the traditional amputation sites have been adhered to fairly closely. It has been suggested,⁴ however, and, we believe, with merit, that lower amputation levels in the leg may be selected. Despite the minimal circulation present in arteriosclerotic extremities, refrigeration, by reducing tissue metabolism and lessening the demands on the available blood supply, permits removal of a

of treating compound fractures was assiduously carried out, including wound débridement, introduction of sulfanilamide powder into the wound and prophylactic tetanus-gas gangrene antitoxin. Three days later, the temperature was 104.2°F., and the pulse 170 (Fig. 6). The wound was inspected and the arm was found to be swollen, with no pulse at the wrist and crepitation of the tissues. A diagnosis of gas-bacillus infection was made. The wound and adjacent soft tissues were opened widely, irrigations of hydrogen peroxide were instituted, and therapeutic doses of gas-gangrene antitoxin (10,000 units every 4 hours) x-ray and sulfanilamide were given. Despite all treatment, the infection rapidly spread upward and the arm became gangrenous. Permission for amputation was refused by the patient's parents. Four days later, he was practically moribund, with a rectal temperature of 103°F., a pulse of 160 and an extension of the infection into the axilla and anterior chest wall. Consent for amputation was finally obtained.

A tourniquet was applied to the upper arm just above the grossly sloughing area, and the extremity below the tourniquet was packed in ice. Within 2 hours, the patient's condition improved remarkably. He became brighter and less toxic appearing, and showed a drop in temperature and pulse rate. Because of this slight improvement, amputation was delayed for approximately 20 hours more, in the hope

that further improvement would enhance the chances of recovery (Fig. 7). At that time a quick guillotine high-arm amputation was done in the patient's bed. He stood the operative procedure well. Convalescence was entirely uneventful, and he was discharged home in 3 weeks.

The refrigeration amputation was probably not the only factor in this patient's recovery. It seems certain, however, that had any other anesthetic agent been used he would not have survived.

CASE 2. J. B., a 71-year-old man, was admitted to the hospital on July 26, 1941, with a diagnosis of fracture of the left patella. Five days later, under spinal anesthesia, an open reduction was performed with silk-suture technic. Six days later, sepsis in the wound was observed and drainage was instituted. Improvement occurred for a time, but sepsis then progressed, and wide incision and exploration were done, again under spinal anesthesia, on November 17.

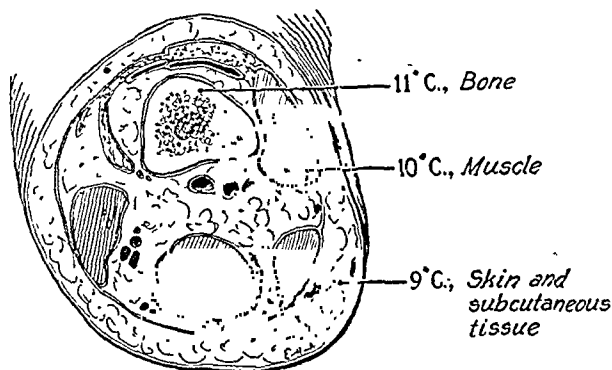


FIGURE 3. Temperatures Taken at Skin, Muscle and Bone Levels in the Amputated Stump following Refrigeration.

This figure demonstrates that cold penetrates to sufficient depth within two or three hours to ensure adequate anesthesia for amputation.

Necrotic fragments of the patella were removed and it was noted that the joint cartilage was completely destroyed. X-ray films showed destruction of the upper end of the tibia and the lower end of the femur. The patient ran a stormy postoperative course, including pneumonia at the bases of both lungs, and continued to run a spiking temperature between 101 and 103°F. He went downhill rapidly, and a refrigeration amputation of the thigh was decided on. After 4 hours of refrigeration, the patient's condition did not improve and death seemed imminent. Amputation was postponed. After another interval of 3 hours (7 hours of refrigeration), his condition seemed favorable enough to warrant operation.

Thigh amputation was done painlessly and without any perceptible change in the pulse or blood pressure. The stump was left open and traction sutures were applied to the skin. The postoperative course was uncomplicated. No further plastic procedure was necessary on the stump, and the patient left the hospital in 6 weeks.

This case is typical of the old, bad-risk patients who, because of sepsis and arterial insufficiency, withstand poorly major operative procedures on the extremities.

Postoperative management is predicated on the principle that temperatures may be reduced or elevated according to the patient's needs. The temperature of the stump is allowed to return to normal by the gradual withdrawal of the ice bags placed about the stump. If, on the other hand, there is any tendency to sloughing or infection of wound edges, further reduction of tissue metabolism to a level for which the existing blood supply is adequate should be initiated.

Healing

Most wounds from refrigeration amputation when tightly closed heal per primam, and the percentage of first-intention healings is comparable to that after similar operations done under other anesthetics. It is to be emphasized, however, that refrigerated incisions heal more slowly than others, because of the known tendency of cold to inhibit agglutination of wound surfaces. Sutures should therefore not be removed from wounds for fifteen to twenty days. Raising the temperature of the stump as rapidly as possible promotes rapid healing, but this is not justifiable because of the risk of incurring sloughs. Slow healing is better than no healing at all.

Clinical Data

In the ten-year period from 1930-1939, there were at the Boston City Hospital 162 cases of major gangrene of the extremities from different causes that were deemed inoperable, either because of the spread of the disease itself or because of other factors, such as old age and cardiorenal, cerebral or other complications (Table 1). The mortality rate was 100 per cent. It was believed that if a certain percentage of lives could be salvaged from a comparable group of bad-risk patients, the refrigeration method would be decidedly worth while. In addition, the mortality rate on 270 cases of major gangrene operated on at this hospital between 1930 and 1939 was 53 per cent. Although no attempt is made here to analyze this high mortality figure, and although it is certain that many poor-risk cases were included in the group, it is our conviction that it is excessively high.

Fifty-four patients were refrigerated. Of these, 50 came to amputation and 4 died before operation. The latter were moribund on entry. The ages

TABLE 1. Results in Cases of Major Gangrene, with and without Amputation and with and without Refrigeration.

TYPE OF CASE	NO. OF CASES	NO. OF DEATHS	PERCENTAGE MORTALITY
Unoperated cases, with complications (1930-1939).....	162	162	100
Operated cases, with and without complications (1930-1939).....	270	142	53
Unoperated cases, with refrigeration (1940-1943).....	4	4	100
Operated cases, with refrigeration (1940-1943).....	50	16	32

ranged from fifty to ninety, with 1 patient in the second decade, 8 in the sixth, 17 in the seventh, 24 in the eighth and 4 in the ninth. Forty-nine patients suffered from advanced arteriosclerotic gangrene with complications of diabetes and sepsis (16 cases) recent cerebral accidents and cardiac failure (2 cases) or other serious infirmities.

The immediate salutary effect of chilling of tissue on the more prominent signs and symptoms was most striking. Relief of pain was observed in every case and without the aid of the customary medica-

tion It is well known that sudden arterial occlusions, as from embolism, are most painful and that great discomfort persists for many hours after the initial obstruction. It has been in this group that the relief of pain has been most dramatic. Shock has always been an outstanding and disturbing feature of thigh amputations, both during and after operation. In addition to operative trauma, general and spinal anesthesia, particularly the latter with its frequent attendant fall in blood pressure, contribute greatly to secondary surgical shock. This phenomenon is not observed in refrigeration operations

from the figure of 53 per cent on operated cases during the ten-year period 1930-1939. In a series of 50 unselected cases in another municipal hospital, Crossman et al,⁵ have shown a mortality of 13 per cent under the refrigeration method, with only 1 death in the last 30 cases, a mortality of only 3 per cent. It may be pertinent to apply the tourniquet-refrigeration method as a routine procedure in all cases coming to major amputation in large municipal institutions.

The causes of death in this series are interesting, since most of the fatalities occurred after the pa-



FIGURE 4 Simple Circular Amputation below the Tourniquet Site. The tourniquet remains on during operation and is removed just before closure of the fascia

There was little if any pulse or blood pressure change in this series, in fact, shock was practically absent in 50 cases. The progress of gangrene and sepsis was notably inhibited in 48 cases by the application of cold. In several of these cases a tourniquet and refrigeration were applied for as long as twelve hours without progress of infection or gangrene and with first intention healing following amputation. At first, doubt was entertained as to the effects of low temperatures on wound healing and breaking down of the operative site was expected. For this reason, the first few amputations, because of gangrene and sepsis, were done by the guillotine method, with secondary closure performed later. Subsequently, all wounds were tightly closed except those in which there was an unusual amount of rapidly ascending infection.

In 50 cases of amputation, there were 16 deaths, a mortality of 32 per cent (Table I), and a salvage, in terms of 1930-1939 figures for unoperated cases, of 68 per cent. In addition, by this method there has been a reduction of 21 per cent in mortality

patients were over the effects of their operation, with stumps adequately healed, and were sitting up or out of bed or ready to be discharged.

Two patients died from gas-bacillus infection in the stump. These were among the early patients refrigerated and represented consecutive cases from the same ward. They had not been given preliminary anti gas bacillus serum. At the present time, not only does every case get prophylactic polyvalent anti gas-bacillus serum, but sulfanilamide is put in the wound before closure. The other 14 deaths were due to various manifestations of cerebrovascular accidents, sudden cardiac failure or pulmonary embolism.

Despite the lack of apparent relation to the anesthetic agent, these deaths must statistically be held against the operative procedure.

In a more recent study of 33 consecutive cases of major gangrene at the Boston City Hospital, taken as they came to the surgical services, including both good and bad risks, there was a total of 4 deaths, a mortality of 12 per cent — a decided contrast, al-

though in a much smaller series, to the 1930-1939 mortality rate of 52 per cent.

Refrigeration without Amputation

Local chilling of tissues without application of the tourniquet was attempted in a series of cases in which there was some factor of circulatory insufficiency that had not progressed to the point where loss of the limb was indicated. The method used was either the application of ice bags or immersion of the limb in crushed ice for several hours. It was hoped that the lowered oxygen demands of the part thus affected might avert impending gangrene, inhibit sepsis or retard thrombosis. This

This case suggested the application of reduced temperature to all extremities in which there were progressive occlusion of the peripheral arterial trunks and signs of imminent gangrene. At the present time, all cases of arterial insufficiency in the extremities, from whatever cause, are treated by the application of cold, and no longer by the old, familiar heat cradle encasing the time-honored 50-watt bulb, which so often resulted in the rapid spread of the gangrenous process. In this group may be mentioned vascular insufficiency brought about by arterial thrombosis or sudden arterial occlusion due to emboli, in which the time interval of four to five hours for doing a successful arterial embolectomy has passed, and frostbite of whatever

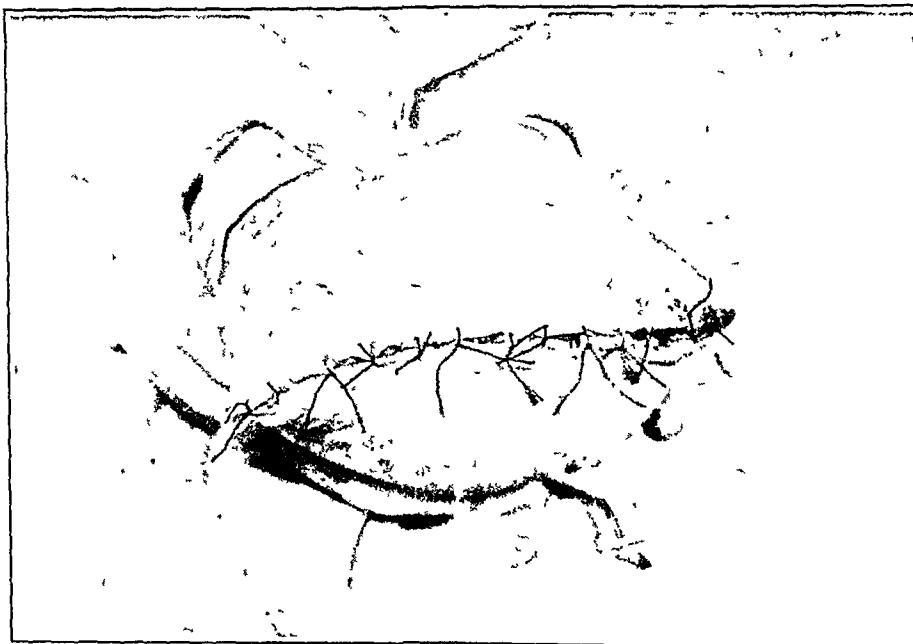


FIGURE 5. *Wound Closed without Drainage.*
The sutures should remain in place for fifteen to twenty days because of delay in wound healing due to cold.

series is too small for the results to be convincing, but it nevertheless suggests certain important trends in the therapy of these conditions.

In some of these cases, the results were extremely gratifying; in others, they were frankly disappointing. On the encouraging side was a moderately advanced case of scleroderma, with deep infection of the fascial space in the hand. The employment of hot compresses and hot soaks resulted in a rapid spread of sepsis, with marked bleb formation. Since a state of deficient blood volume in the sclerodermic extremity was being dealt with, it became evident that increased oxygen demands engendered by the application of heat were causing a progressive spread of infection. A reduction in temperature, by burying the forearm and hand in ice and alternating this procedure with ice bags, produced a gradual but definite recovery.

severity. In this connection the emphasis that has been put by Webster, Woolhouse and Johnston⁶ on the effect of reduced temperature in the treatment of immersion foot deserves mention. These observers noted a tremendous tissue reaction when patients suffering from immersion feet were exposed to ordinary room temperatures. There was edema, ecchymosis and bleb formation of the skin, suggestive of the reaction of feet with impaired blood supply that are developing gangrene. Reduction of temperature to 6°C. below normal skin temperature by the application of ice bags was the best single therapeutic measure used in combating this condition.

In the presence of frank gangrene of the extremities, with or without sepsis, refrigeration definitely retards the progress of gangrene and infection. In no cases in our experience, however, has

reduction of temperature averted amputation when devitalization of a part had once occurred. It has

Several patients with deep venous thrombosis of the lower extremities, all candidates for ligation and

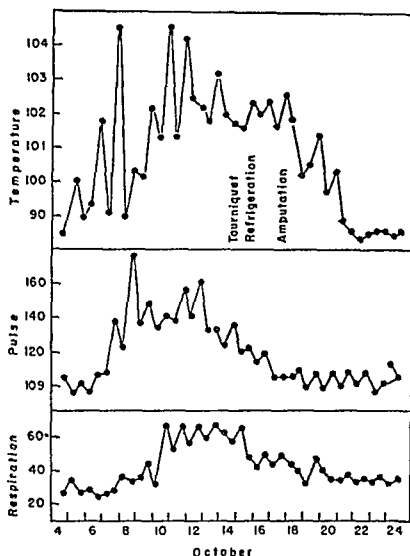


FIGURE 6 Chart Showing Rapid Improvement after Refrigeration and Amputation

been interesting to observe that when gangrenous limbs are exposed to ordinary room temperatures

division of the femoral vein, according to the usual requirements for such a procedure, were treated by



FIGURE 7 Appearance of Arm Prior to Operation
Infection had spread beyond the tourniquet to the anterior chest wall

after refrigeration, gangrene progresses rapidly. A return to decreased temperature slows the process.

A local chilling of the tissues. All improved without further treatment. This observation is not par-

ticularly convincing, since many such cases improve with rest alone. It may be of value, however, in suggesting that prolonged cold, without freezing, inhibits thrombosis. Our preference in the treatment of deep venous thrombosis, we hasten to add, is still for interruption of the proper deep venous channels.

Refrigeration has been suggested as a valuable adjunct to the treatment of various injuries and burns. The advantages of cold in preventing toxic absorption, inhibiting bacterial growth and reducing pain, shock and edema seem to make this method desirable in traumatic cases. Its influence in military surgery, particularly under conditions of active warfare, appears to be of inestimable value. Its application is strongly urged.

SUMMARY AND CONCLUSIONS

The use of refrigeration as an anesthetic agent in major amputations of the extremities is a sound surgical procedure. It is particularly applicable to poor-risk cases, since it inhibits shock, relieves pain, retards infection and thrombosis.

A series of 50 bad-risk patients treated by the tourniquet-refrigeration method showed a marked reduction in mortality under that of a comparable series either untreated or treated by some other method. A later series of 33 patients, both good and bad risks, showed a marked reduction in mortality after refrigeration amputation.

Further possibilities in the use of reduced temperatures in the treatment of peripheral vascular disease and of injuries and in military surgery have been discussed.

I am indebted to Dr. George Miller, resident surgeon on the Third Surgical Service, Boston City Hospital, for his assistance in compiling the data used in the preparation of this paper. 270 Commonwealth Avenue

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THE TREATMENT OF PULMONARY EDEMA DUE TO GAS POISONING IN WAR AND IN CIVILIAN LIFE*

With Special Reference to the Use of Positive-Pressure Respiration

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THE purpose of this paper is to outline a tentative program of treatment for patients who develop edema of the lungs following exposure to irritant gases.

For the most part, pulmonary irritants are considered acid gases, since they owe their physiologic effect to the fact that they are acids or behave like acids under the conditions of their use. They include hydrogen chloride, bromide and fluoride, chlorine, fluorine, bromine, sulfur dioxide and certain oxides of nitrogen, as well as phosgene, di-phosgene and chloropicrin. There are other less common pulmonary irritants such as ammonia and formaldehyde. The carbonyls are also included in this group because of their property of depositing finely divided particles of metal in lung tissue, thus inducing an intense pulmonary irritation and edema. The properties of these substances determine their behavior in the body. Thus, their solubility in water is a determining factor in the location of their action. Highly soluble gases, such as chlorine, ammonia and sulfur dioxide, exert their primary effects on the upper-respiratory tract and, if exposure has taken

place to low concentrations or for not too long time, the damage may be confined almost entirely to the nose and throat. Exposure to higher concentrations or for a longer period of time results in characteristic edema of the lungs, without extensive necrosis of the upper respiratory tract. The chief injury associated with inhalation of phosgene is apt to be in the lungs, in which congestion and widespread edema ultimately develop.

Chlorine and phosgene are sometimes employed as war gases for their destructive effect, but they also have been known to cause pulmonary edema in civilian life as the result of disasters or industrial accidents. For example, when carbon tetrachloride (Pyrene) is used in fire extinguishers in enclosed spaces, it may be sprayed on hot metal, with a resultant liberation of phosgene. Edema of the lung may thus take place if the concentration of the phosgene evolved is such as to cause damage to the lining of the respiratory passages as well as to the pulmonary epithelium.

Phosgene is a colorless gas at temperatures above 8°C., with an odor of musty hay. It is soluble in water, and hydrolyzes to hydrochloric acid and carbon dioxide. Since there is little immediate irritation to the larynx and trachea, the gas may reach the lungs in high concentrations. Thrombosis of the blood vessels, concentration of blood in the per-

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monary capillaries, edema in the alveoli and in the alveolar septa and rupture of the alveoli constitute the main pathologic effects. If the patient survives the pulmonary edema, bronchopneumonia frequently follows and may be the cause of death.

In general, the pathologic condition found after inhalation of irritating gases is that of intense congestion and inflammatory edema, followed by a cellular exudate, with a varying amount of necrosis of the lining membrane of the respiratory passage. If death does not take place, there may be organization of the exudate within the alveoli and bronchi, with the production of bronchiectasis, pulmonary fibrosis and perhaps chronic suppurative lesions. The variations in pathologic effects exercised by the several gases have been fully described by Winternitz and his associates¹⁻⁵; Haggard⁶ and Henderson and Haggard⁷ have pointed out the similarity in toxicologic action of all the respiratory irritants and have stressed the difference in symptomatology as due to the location of their action and the relative solubility of the irritating gases. A gas that is highly soluble in water is readily taken out of the inspired air by contact with the first moist tissue it reaches, and therefore the upper respiratory tract bears the brunt of action. On the other hand, a gas with a low solubility in water is slower to liberate its irritant principle, and the most important damage usually takes place in the pulmonary epithelium. Carlisle⁸ has listed the following gases that have resulted in pulmonary edema in the course of industrial accidents: the oxides of nitrogen, phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, methyl bromide, chlorine, cadmium and dust from certain alkaloïds.

Sulfur dioxide is an effective refrigerant but is a respiratory irritant that has been said by Hamilton,⁹ Norris and Landis,¹⁰ Gordon¹¹ and Kehoe et al.¹² to be the cause of deleterious effects, although no lasting harm after exposure was observed by McCord.¹³

The symptoms depend on the solubility of the gas, as mentioned above. In some cases cough and tightness and pain in the chest are followed by shortness of breath and expectoration of seromucus, such as after exposure to the fumes of chlorine, nitric acid, ammonia and chlorpicrin. In other cases, such as after exposure to phosgene, the patient may reveal no symptoms for two to four hours except watering of the eyes and catching of the breath. Later, tightness of the chest, painful coughing and the characteristic symptoms of edema of the lungs may manifest themselves, with moist rales and bloody or frothy sputum. If the concentration of phosgene is moderately high, symptoms of pain in the chest and coughing may assert themselves soon after exposure.

Kehoe¹⁴ has mentioned four types of effect of exposure to irritant gases. The effect of exposure to extremely high concentrations may be immediate

death from anoxia due to direct damage to the respiratory membranes, rendering them impermeable to normal respiratory gases. Rapid absorption of the poison may be the chief factor in death by producing circulatory collapse (vagus shock). Differing only in degree from the above is an exposure to a high concentration of an irritant gas that results in extensive damage to the pulmonary and upper respiratory tissues, including acute hyperemia, and destruction of tissue (coagulative necrosis). If death does not take place promptly, acute emphysema of the lungs, with general acute interstitial edema, ischemia and coagulation necrosis, may result, with death the ultimate outcome. The moderate nature of a pulmonary injury makes possible an opportunity for survival. Irritative effects in the upper respiratory tract and acute pulmonary edema may be present, with threatened asphyxia or later complications, such as bronchopneumonia. Lastly, mild exposure to respiratory irritants for comparatively short periods may result in injury mostly limited to irritation of the eyes and upper respiratory tract, with redness and lacrimation, coughing, sore throat, huskiness, loss of the voice, nosebleed, moderate chest pain and excessive coughing. Recovery may take place with little or no treatment, but in some cases the condition progresses to such an extent that the patient is placed in the category described above.

Since this discussion is confined to the treatment of pulmonary edema, the chronic effect of gas poisoning and the manifestations of chronic gas poisoning will not be considered. The nature and severity of edema of the lungs after exposure to gas poisoning is difficult to predict, since the pathologic condition is subject to considerable variations depending on the gas concerned as well as on its concentration and the length of exposure. The onset of pulmonary edema may be prompt, or it may be delayed for as long as twelve hours. In the upper respiratory tract an inflammatory reaction may take place with a serosanguineous discharge; later, ulceration and hemorrhage may manifest themselves. In certain cases the bronchi show ulcerations and necrosis and plugs of debris obstruct the smaller air passages. The lungs may be filled with edema, and the trachea as well. A watery and at times serosanguineous fluid may be present, with, later, a purulent or fibrinopurulent exudate. Edema of the alveolar cells and interstitial tissues, with coagulation necrosis, hemorrhage, thrombosis and infarction of the blood vessels, may be present in varying proportions at different sites of the lungs. Damage is likely to be spotty rather than general. This may be caused to some extent by bronchial obstruction, due either to inflammation or to bronchial spasm, which limits the passage of contaminated air to certain parts of the lungs. Both petechial and confluent hemorrhages take place. Large or small areas of deeply congested lung tissue are seen at autopsy,

with a thin, sanguineous fluid dripping from the surface. If death takes place at a later stage of the development of pulmonary edema, chronic bronchitis, bronchiectasis and abscess of the lungs may be found.

As a result of swelling of the alveolar cells, the absorption of oxygen at atmospheric pressure proceeds at a slower rate than normally and unoxygenated blood passes into the aortic stream. The narrowing of the smaller bronchi results in incomplete ventilation of some of the alveoli, with accentuation of anoxia. Finally, the presence in the alveoli and the respiratory passage of serum and mucus further complicates ventilation of the alveoli.

In cases in which there is constriction of the bronchi, due to spasm and inflammatory swelling of the mucous membrane, an increased respiratory effort takes place, with a resultant increase in the negative pressure within the lung during inspiration. Any increase in negative intrapulmonary pressure tends to aggravate edema of the lungs by producing a suction action on the pulmonary epithelium. The increased ventilation engendered by anoxia is apt to be followed by a lowering of the carbon dioxide tension in the blood, the acid-base equilibrium shifting to the alkaline side. In severe asphyxia, however, acidosis takes place, the low pH being due to incompletely oxidized acid metabolites.

When pulmonary edema has been present for a considerable period of time, the loss of serum in the lungs results in concentration of the blood, and the diminished blood volume and increased viscosity promote stasis and capillary thrombosis. This circumstance is an additional factor that makes for tissue anoxia and ultimately throws an increased burden on the heart, owing to the increased resistance in the pulmonary circuit. Death may ultimately take place from right-sided heart failure, peripheral circulatory failure or bronchopneumonia.

The routine prescription of rest, warmth and inhalation of oxygen-enriched air is helpful to a certain percentage of patients. The inhalation of air with a high percentage of oxygen, such as 50 to 70 per cent, diminishes the severe anoxia in cases of outspoken pulmonary edema and this protects the patient from a cardiorespiratory failure that might otherwise ensue. Furthermore, the volume of ventilation is diminished under these circumstances by inhaling air with a high oxygen concentration and in this way the pathologically elevated negative intrapulmonary pressure is diminished and the suction effect of a high negative pressure on the lungs is prevented.

In many cases of pulmonary edema treated with rest, warmth and the inhalation of air with a high oxygen concentration, the passage of serum from the capillaries into the alveoli continues and drainage through the respiratory passageway is impeded, with the ultimate development of bronchopneumonia

and death. The administration of positive pressure to combat edema of the lungs produced by gas poisoning was suggested by Barach, Martin and Eckman¹⁵ in 1938 in a paper dealing with the therapeutic advantages of positive pressure in the treatment of clinical pulmonary edema. Mention was there made of a case of edema of the lungs described by Norton¹⁶ in 1897 in which a rapid clearance of the edema took place with the use of the Fell-O'Dwyer forced-respiration apparatus. Although a theoretical discussion of the mechanism was not given in Norton's report, the clinical result was carefully described and was unmistakably the result of the introduction of a laryngeal tube and the application of forced respiration under positive pressure. No previous studies on the application of positive pressure in the treatment of irritant pulmonary edema due to gas poisoning have been reported.

The use of positive pressure for the treatment of clinical pulmonary edema was suggested by Plesch and an apparatus for providing it was used by Poulton¹⁸ in cases of paroxysmal dyspnea—so called "cardiac asthma"—and of bronchial asthma. No benefit was obtained when there was generalized heart failure.

Barach¹⁹ and his colleagues developed an apparatus for the administration of positive pressure, originally for the treatment of bronchial obstruction in intractable asthma and obstructive lesions of the respiratory passageway. These comprised a mask with a closed-circuit apparatus, a hood that fitted over the patient's head and made closure at the neck and a mask in which the patient breathed during expiration against resistance, provided by exhalation at first through a rubber tube placed in water to a depth of 3 to 6 cm., and later through a variably narrowed orifice attached to the mask. The methods of applying positive pressure were found to be effective in many severe cases of edema of the lungs occurring during the course of pneumonia and acute failure of the left ventricle.

In 1909, Emerson²⁰ showed that pulmonary edema produced by the intravenous injection of adrenalin into rabbits could be consistently removed by artificial respiration through a tracheotomy tube in which the lungs were gently distended and then allowed to collapse. In 1917, Auer and Gates²¹ confirmed these results and showed that tracheal stenosis accentuated the edema caused by adrenal congestion and edema of the lung as the result of tracheal stenosis were shown by Moore and Bing to be due to obstruction during the inspiratory cycle. Kernan and Barach²² confirmed these observations and showed that expiring against a pressure of 4 to 5 cm. of water created no significant change in the lungs, whereas inspiring against a negative pressure of 4 to 6 cm. caused congestion and pulmonary edema in the lower part of both lungs, with areas of emphysema at the periphery. The negative intrapleural pressure became steadily elevated with

animals were made to inhale through a constricted orifice. This elevation was decreased by the inhalation of a helium-oxygen mixture or by the administration of positive pressure during inspiration. The significant factor in the production of pulmonary congestion and edema due to narrowing in the respiratory passage appeared to be the pathologically elevated negative intrapleural pressure, which resulted first in an increase in pulmonary blood flow and later in a direct cupping action on the pulmonary capillaries. In experiments on animals, Barach, Martin and Eckman¹⁵ showed that edema of the lungs produced by intravenous injection of adrenalin could be prevented by inhalation of air under positive pressure, which raised the intrapleural pressure toward the atmospheric pressure during expiration. In this experiment it was demonstrated that no heightened negative pressure existed in the intrapleural space, and that the effectiveness of positive pressure was due to the direct opposing pressure on the capillary epithelium in the lungs of a physical force that tended to counteract the internal hydrostatic pressure in the pulmonary capillaries. Another influence was that the positive pressure retarded, to some extent, the inlet of blood into the right side of the heart.

It may be mentioned at this point that Meltzer²⁴ in 1878, said that the origin of pulmonary edema was due to a disproportion between the working power of the left ventricle and that of the right ventricle of such a character that, the resistance being the same, the left side of the heart was unable to expel in a given unit of time the same quantity of blood as was the right side.

The effect of respiration under positive pressure of 3 to 10 cm. of water in normal persons and in patients with congestive heart failure and asthma has been studied by me and my colleagues.^{15, 19, 23} The venous pressure was consistently elevated. During the application of a pressure of 6 cm. the venous pressure was elevated 2 to 3 cm. The circulation time in normal young adults was slightly prolonged, but in patients with heart disease the slowing was as much as ten to fifteen seconds. Although prolongation of the circulation time did not occur in all cases, the change when it took place was more marked in cardiac patients than in normal persons, in whom the prolongation when breathing against a positive pressure of 6 cm. averaged three and a half seconds. In a normal adult the effect of breathing against a positive pressure of 6 cm. resulted in an increased amount of air in the lungs, — approximately 400 cc., — with a lowering of the midposition of the lungs and a lengthening of the vertical diameter of the chest. The only contraindication to the use of positive-pressure respiration noted by Barach, Martin and Eckman¹⁵ was that of peripheral circulatory failure. Since in shock a deficient return of blood to the right side of the heart is already present, the high intrapulmonary pressure

produced by inhalation of air or oxygen under positive pressure may further prevent the customary entrance of blood into the right auricle. The clearing of pulmonary edema in clinical cases of edema of the lungs was later confirmed by Boothby, Mayo and Lovelace²⁵ and others.²⁶

In summary, the effects of positive-pressure respiration include an increased intrapulmonary pressure, which lowers the pathologically elevated negative pressure in the lung during respiratory obstruction (Fig. 1); an increase in systemic venous pressure amounting to 40 to 50 per cent of the applied pressure; a prolongation of the circulation time, which is notably more marked in patients with congestive heart failure than in normal subjects; an increased volume of air in the lungs, with a lowering of the midposition of the lungs and an increase in the vertical diameter of the chest; and a decrease in the transverse diameter of the heart, shown in roentgenograms of rabbits' hearts.

The favorable results of the administration of oxygen and helium-oxygen mixtures under positive pressure in the treatment of ordinary cases of edema of the lungs suggest that it would be valuable in the treatment of irritant gas poisoning.¹⁵ In a personal communication, Carlisle⁶ has reported that the administration of oxygen under an expiratory positive pressure of 1 to 6 cm. of water is the most effective method of treating and preventing pulmonary edema due to irritant gases. No patient exposed to lung irritants has been lost since this procedure was adopted. Over 300 cases of such exposure have been treated, and at least 25 manifested signs of edema.*

The technic of applying positive pressure may consist of the use of the hood designed for the treat-

*Since this paper was prepared, Carlisle has made the following statement (*J. A. M. A.* 123 947, 1933):
Without significant bronchiolar obstruction and before advanced

from our own experience that the use of the 1 to 100 epinephrine solution combined with the administration of oxygen under positive pressure of 1 to 6 cm. of water may be recommended for active treatment of the advanced stages of pulmonary edema caused by certain noxious gases. In our experience this has been a far more effective method of handling fatal pulmonary edema than any of the procedures hitherto suggested. We find that on check of our records for the past year and a half, we have had 316 cases in which only this method of treatment has been employed.

Furthermore, Evans (*New York State J. Med.* 43 2301-2305, 1943) has commented on the use of positive pressure in treating the irritant pulmonary edema that developed in victims of the Cocoanut Grove Fire in Boston. He states that good results were obtained with the employment of oxygen under positive pressure and that the results in 4 cases were "rather spectacular."

The following notes on a case of irritant pulmonary edema were kindly transmitted to me by Dr. E. A. Rovenstein, of New York City, who treated a patient with positive pressure. The significance of this case is considerable in the application of an expiratory positive pressure of 5 cm. was followed by a swift clearing of edema, and seemed specifically responsible for recovery.

A middle-aged woman admitted in the early morning on February 19, 1943, had been exposed to fumes of a chemical (undetermined, but may have been dimethyl sulfate). Exposure was about 9:00 p.m. the evening before, with no symptoms for a couple of hours. Laceration and burning of the eyes and throat were noted. Later the patient became short of breath. On admission she was dyspneic and had severe pain, copious secretions and some cyanosis. The respiratory rate was 30 to 40, and the heart rate 120. Her condition rapidly became worse.

Oxygen was administered through the nasopharynx. An hour later there were obvious pulmonary edema, extreme cyanosis, marked venous engorgement and severe pain. Her condition was rapidly becoming alarming. An O₂ M. positive-pressure mask was adjusted at 5 cm. pressure, the result was dramatic, and within 15 to 20 minutes the edema had cleared. A phlebotomy (200 cc.) was completed after improvement was noted from oxygen therapy. The subsequent recovery was essentially uneventful.

ment of obstructive dyspnea, in which a positive pressure of 3 to 6 cm. is applied, during both inspiration and expiration. This method is the most comfortable and effective one for positive-pressure breathing. Dyspnea is relieved, since the pressure during inspiration results in a swift lowering of the intrapleural and intrapulmonary negative pressure and, during expiration, in a maintenance of a wider lumen of the bronchial tree (Barach and Swenson²⁷).

in which expiration is conducted through one of a series of variably constricted orifices, the degree of constriction determining the degree of positive pressure exerted during expiration, so that a pressure of 1 to 4 cm. in expiration during quiet breathing is obtained (Barach and Molomut²⁸). When the volume of ventilation is notably increased, a pressure of 4 cm. through the proper orifice results in a higher expiratory pressure. Recent measurement

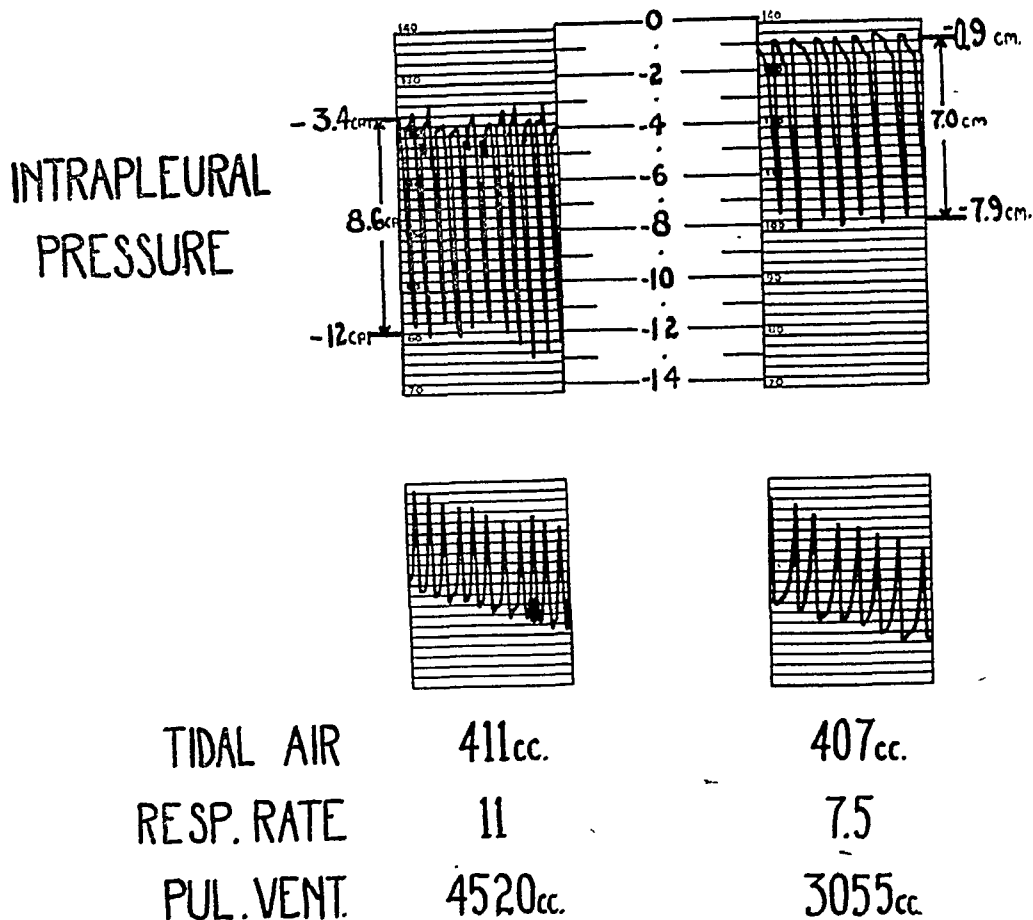


FIGURE 1. Intrapleural Pressures and Tidal-Air Volumes in a Dog Breathing through a 5-Mm. Orifice.

The tracings on the left were made with the air at atmospheric pressure; those on the right, with the air at 5.5 cm. water pressure.

The use of the mask with a closed-circuit re-breathing apparatus was employed in 1936 before the development of the hood. The apparatus is more cumbersome than the hood, since the removal of heat, carbon dioxide and moisture is necessary and depends on the continuous use of a motor-blower unit. A mask was then devised in which expiration takes place through a rubber tube inserted 3 to 6 cm. under water (Fig. 2).^{*} The length to which the connecting tube is placed under water determines the extent of positive pressure within the mask and therefore the degree of pressure exerted on the respiratory passage and the inner surface of the lungs. Later, a simpler device was used

have shown that during expiration through narrowest orifice an expiratory pressure of 1 to 12 cm. may result. The so-called "meter" with a pressure disk containing variably constricted orifices for expiration is the most convenient apparatus for administering positive pressure, but the degree of pressure actually received actually varies with the volume of ventilation, as described above. A rubber tube extended into a water bottle gives a more accurate expression of the positive pressure, but is more cumbersome. A metered positive-pressure mask may be calibrated by inserting a needle in the mask and connecting it by a rubber tube to a water bottle so that the degree of positive pressure can be accurately determined.

*Manufactured by the Oxygen Equipment Manufacturing Company, Incorporated, New York City.

In the treatment of a case of gas poisoning, both the degree and the duration of positive pressure are determined by a consideration of the factors discussed above. The administration of a positive pressure of 6 cm. may be sufficient to result in disappearance of edema in one to three hours. The pressure may be begun at 3, 4, 5 or 6 cm., depending on the co-operation of the patient. If pulmonary edema disappears during the application of a positive

pulmonary pressure naturally facilitates the inlet of blood into the right auricle. When pressure is applied within the hood, lower pressures should be used, since positive pressure is then exerted on the pulmonary capillaries in both inspiration and expiration. A pressure of 3 cm. of water has been found to be effective in terminating clinical pulmonary edema, although one of 4 to 5 cm. may be used in severe cases. Experience with the hood has



FIGURE 2 Mask with Positive Pressure in Expiration.

pressure of 3 to 6 cm. in a period of several hours, the pressure should be lowered to 2 cm. for one to two hours more. At the end of this time it should be lowered to 1 cm. for one or two hours and then removed. In other cases, if pulmonary edema has cleared, trials should be made of breathing without the mask for a period of five to thirty minutes, and if coughing and edema do not supervene, treatment should be discontinued. In the event that coughing and signs of pulmonary edema recur, the mask should be reapplied and positive pressure used for as long as necessary.

When pressure is applied during the expiratory cycle alone, there is less apt to be any noteworthy interference with the return of blood to the right side of the heart, since blood may enter the lungs during the inspiratory cycle, in which a negative intra-

been limited to cases of clinical pulmonary edema, only masks having been employed by Carlisle for the treatment of gas poisoning.

Although the administration of air containing 40 to 100 per cent of oxygen may be indicated in frank pulmonary edema in which severe arterial anoxia is present, the use of positive pressure with atmospheric air may be all that is required in the prevention of pulmonary edema after gas poisoning. Further studies are necessary to confirm this opinion. If gas poisoning has occurred in combat areas or in localities where oxygen in cylinders is not immediately available, the metered positive-pressure mask may be used by detaching the collecting bag and the rubber tube. Under these circumstances the patient inspires through the inspiratory valve that connects with the outside air; during expiration the

valve closes and the expired air passes outward through a constricted orifice representing a pressure of 2 to 10 cm. of water. Since the permeability of the pulmonary capillaries as well as of the capillaries in the respiratory passage may be altered so as to produce oozing of both serum and mucus, inhalation against positive pressure tends to prevent the onset of the syndrome by neutralizing the internal hydrostatic pressure within the capillaries. Further experience is necessary to determine the range of effectiveness of this method. A three-hour period of breathing against positive pressure is recommended, followed by a gradual lowering of the pressure to that of the atmosphere for one to three hours longer, depending on an estimation of the severity of exposure.

If the metered mask is used with air, the inner surface of the mask should be equipped with an additional emergency inspiratory valve so that a plentiful inlet of air will take place without negative pressure's developing within the mask, even under conditions of severe dyspnea. If mixture of air and oxygen are to be provided, the metered mask, equipped as it is with an injector attached to the regulator, should be employed. With this apparatus oxygen and air are mixed at the regulator and a high flow of the oxygen-enriched air is passed into the collecting bag. The B.L.B. mask²⁹ can be used for the treatment of pulmonary edema if the flow of oxygen used is sufficient to keep the rebreathing bag from completely collapsing during inspiration. If the bag collapses, a negative pressure develops while air is being drawn through the sponge-rubber disks. Another way of using this apparatus without negative pressure's developing in the mask is to fit it so loosely to the face as to do away with the need for the disks.

Since the prolonged administration of 100 per cent oxygen is itself productive of pulmonary edema in animals, and since the specific therapeutic measure is the application of positive pressure, the employment of air containing 40 to 70 per cent of oxygen under positive pressure is recommended rather than that of 100 per cent oxygen. In the prevention of pulmonary edema, inhalation of air under positive pressure is likely to be adequate. In the absence of a mask, the patient should be instructed to exhale through partially closed lips or through a partially closed glottis, as in grunting respiration, thus naturally increasing the intrapulmonary pressure during expiration.

Another procedure of value is the inhalation of the nebulized spray of 1 per cent epinephrine or 1 per cent Neo-Synephrine at intervals of two to three hours. The former is especially valuable in cases of bronchial spasm, and the latter in patients in whom the congestion of the airway is the result of edema. Although the nebulization of these solutions may be accomplished to some extent by hand bulbs, a more effective method is the passage of 5000 cc. of oxygen from a high-pressure cylinder into

a nebulizer containing 0.5 cc. of 1 per cent epinephrine solution or 0.5 to 1.0 cc. of 1 per cent Neo-Synephrine solution (Richards, Barach and Croxwell³⁰). These drugs should be administered by inhalation, the end of the nebulizer being held with the mouth, at intervals of two to three hours. The enlargement of the diameter of the bronchial tree either by diminishing bronchial spasm or by vasodilation of the mucous membrane, may be of definite help in decreasing the negative pressure necessary to inhale either air or the therapeutic atmospheric mixture administered.

SUMMARY AND CONCLUSIONS

The inhalation of oxygen and helium-oxygen mixtures under positive pressure has been shown to be of value in the treatment of cases of obstructive dyspnea and acute pulmonary edema commonly seen in the practice of medicine. The only contraindication to positive-pressure respiration described is the presence of shock.

The employment of positive-pressure respiration in cases of industrial gas poisoning indicates that pulmonary edema of the lungs may be prevented and, when it has occurred, tends to respond to the administration of positive pressure in a far more successful way than under any hitherto suggested procedure.

A pressure of 3 to 6 cm. of water is usually effective in the treatment of pulmonary edema. If signs of edema have cleared, a gradual reduction of pressure over a period of hours is recommended. Prevention of pulmonary edema after exposure to an irritant gas is advocated by inhalation of oxygen against positive pressure for two to three hours and then institution of trial periods of freedom from positive pressure to determine whether or not edema intervenes. Since pulmonary edema may take place as late as twelve hours after exposure, means for providing positive pressure should be at hand in any case in which known contact with a poisonous gas has occurred.

The inhalation of a spray containing 0.5 cc. of 1 per cent epinephrine is helpful in those cases in which bronchial spasm is present, and inhalation of 0.5 to 1.0 cc. of 1 per cent Neo-Synephrine is suggested to increase the lumen of the tracheobronchial tree by vasoconstriction.

In civilian disasters in which phosgene or other toxic gases are liberated, the immediate administration of positive pressure is suggested. Although inhalation of oxygen-enriched air overcomes arterial anoxia, prolongs life, and in some cases saves it, many cases exist in which continued pouring of serum takes place, with impairment of bronchial drainage, secondary infection and bronchopneumonia. Although the sulfonamide drugs may be used to prevent infection, the primary pathological condition is that of a hemorrhagic inflammatory edema, with infection only secondarily produced.

NORMAL AIR ENCEPHALOGRAMS IN PATIENTS WITH CONVULSIVE SEIZURES AND TUMOR OF THE BRAIN*

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WHEN convulsive seizures develop during adult life, the clinician usually considers the possibility that they are a manifestation of some underlying structural lesion in the brain. He therefore studies the patient to exclude the known causes of seizures in adults. Visualization of the ventricles and the subarachnoid spaces by ventriculography or encephalography is one of the tests that are relied on to diagnose or exclude a neoplasm as the cause of the seizures. If the ventricles are found to be of average size and normally placed, the diagnosis of cerebral neoplasm is considered to have been excluded. The fallacy in such an assumption is emphasized by the three case histories given below. These patients had convulsive seizures and each had at least one normal pneumoencephalogram, yet each was eventually proved to have a brain tumor. The duration of seizures before the final diagnosis was established was four, four and a half, and six and three-quarters years, respectively. The first patient had a normal air encephalogram two and a half years after her first convulsion (seventeen months before discovery of the tumor). The second patient had a normal air encephalogram seven months after her first seizure (nearly four years before discovery of the tumor). The third case was the most instructive of all. The patient had two air encephalograms, the first of which, ten months after the first seizure, was interpreted as normal, while the second, ten months later, was considered to show doubtful cortical atrophy on the right, but to be otherwise normal.

CASE REPORTS

CASE 1. H. V., a 38-year-old, married woman, entered the Neurologic Service of the Boston City Hospital on December 1, 1938, because of two generalized convulsions, the first of which occurred 6 weeks before entry. So far as she knew, none of her family had ever had seizures. She herself had had rheumatic fever 15 years previously, and had been deaf in the right ear since an attack of measles in childhood.

Except for a deafness of the middle-ear type on the right there were no abnormal physical findings. The visual fields were normal. Routine blood and urine examinations were normal. The blood nonprotein nitrogen was 26 mg. per 100 cc., and the fasting blood sugar 80 mg. A blood Hinton reaction was negative. Lumbar puncture showed an initial pressure of 60 mm., 2 white cells per cubic millimeter, a total protein of 27 mg. per 100 cc., a gold-sol reaction of 0000000000 and a negative Wassermann reaction. X-ray films of the skull showed evidence of chronic mastoiditis on the right. An electroencephalogram showed no evidence of any focal abnormality.

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§Pennybacker, J., and Meadows, S. P. Normal ventriculograms in tumours of cerebral hemispheres. *Lancet* 1:186-190, 1938.

The patient was discharged on $4\frac{1}{2}$ gr. (0.3 gm.) of Dilantin and $1\frac{1}{2}$ gr. (0.1 gm.) of phenobarbital daily and was seen at regular intervals as an office patient. She continued to have seizures of grand-mal type every 1 or 2 months on a daily dose of Dilantin ranging from $4\frac{1}{2}$ to $7\frac{1}{2}$ gr. (0.3 to 0.5 gm. and $1\frac{1}{2}$ gr. of phenobarbital, which was later replaced by 3 gr. (0.2 gm.) of Mebaral. A supravaginal hysterectomy was performed in January, 1941, because of dysmenorrhea. The removed organ was said to be normal. In the following June, the patient is said to have had a right-sided seizure with loss of consciousness. Because her family had also noticed some personality changes she re-entered the hospital for study in that month.

On examination the patient seemed mentally dull and slow. There was some ataxia of the left leg on a heel-knee test, and the right (*sic*) plantar response was occasionally extensor. An air encephalogram was done on June 9, by the lumbar route. There was some subdural air on the left and a possible shift of the ventricular system to the left, which was decided was an artefact due to rotation of the head. The spinal fluid had a normal protein content and colloidal gel reaction.

In the course of the next $1\frac{1}{2}$ years, the patient continued to have monthly seizures despite treatment with Dilantin and Mebaral. She exhibited a marked personality and later intellectual deterioration, which led to institutionalization in February, 1942. In October, she developed a left-sided hemiparesis, headache and vomiting and was readmitted to Boston City Hospital in November.

At that time the diagnosis of brain tumor was obvious. The patient was drowsy and apathetic and had bilateral papilledema and a left-sided hemiparesis, with a positive Babinski sign and a grasp reflex in the left hand. The cerebrospinal-fluid pressure was 305 mm., but the fluid was otherwise normal. An electroencephalogram showed a right frontal focus. On operation 3 days after entry a right-frontal astrocytoma was found that measured 6 cm. in diameter on surface and extended 5 cm. into the brain substance.

CASE 2. G. L., a 27-year-old, married woman, was admitted to the Neurologic Service of the Boston City Hospital on March 18, 1937, because of three convulsive seizures during the preceding month. Each seizure began with numbness and twitching of the left arm, and possibly the left leg, which was soon followed by loss of consciousness lasting 5 to 10 minutes. In one seizure the patient bit her lip. She seemed drowsy after each seizure and complained of numbness of the lips for an hour or two. There was no family history of epilepsy. The patient had had one convulsion in infancy. She was in the 6th month of her first pregnancy at the time of entry.

Physical examination was essentially normal. There was slight puffiness of both ankles, and the tendon reflexes were generally hyperactive. One examiner noted a sustained clonus of the left patella but this was not confirmed by others and there were no pathologic reflexes, weakness or sensory disturbances. The visual fields were normal. The blood pressure was 120/70. The urine was normal except for the slightest possible trace of albumin on one occasion. There was a mild normochromic anemia, with the hemoglobin 13 per cent (Sahli) and the red-cell count 3,540,000. The blood nonprotein nitrogen was 20 mg. per 100 cc. and a blood Hinton reaction was negative. Lumbar puncture showed an initial pressure of 150 mm., no white cells, a total protein of 13 mg. per 100 cc., a gold-sol reaction of 0000000000, color and a negative Wassermann reaction. X-ray films of the skull were normal.

The patient had one seizure while in the hospital. It began with twitching of the left leg, which was soon followed by loss of consciousness, after which the seizure became generalized. The entire seizure lasted 90 seconds. The patient was discharged on $1\frac{1}{2}$ gr. of phenobarbital daily.

had four or five more seizures during pregnancy, of which at least some consisted only of weakness in the left arm and leg and shaking of the left leg for 2 minutes without loss of consciousness.

Seven months after the onset of symptoms, following a normal delivery, the patient entered another Boston hospital for observation. Extensive blood chemistry studies yielded consistently normal results. Lumbar puncture was repeated and the findings again were normal (initial pressure 120 mm. total protein 34 mg. per 100 cc. and other results as before). X-ray examination of the skull was said to show thinning of the posterior clinoid processes, but an air encephalogram by the lumbar route showed the ventricles well outlined without abnormalities.

The patient continued to have six to ten seizures a year at first — a few days to five months until March 1933 when Dilantin was added to the therapy. At this time she was seizure free for 2½ years and had another attack of numbness in the body which she could not localize, there was no loss of consciousness. A careful neurologic examination at that time was negative except for slight horizontal nystagmus. An electroencephalogram in January 1942 showed a focus of abnormal activity in the right motor area.

The patient tried to take larger doses of anticonvulsant drugs but could not because of dizziness and inco-ordination especially on walking. She continued to have left sided attacks without loss of consciousness, consisting in a feeling of weakness of the affected side, with the occasional addition of twitching of that arm or leg or both. By September she was having about one such seizure a week. Neurologic examination at that time revealed only weakness of the left leg, without abnormal reflexes or sensory disturbances.

Despite the lack of severe or frequent seizures the patient's general condition grew progressively worse and by October 1942 she felt so weak that she stayed in bed most of the time. On November 16, she was operated on and a paramedian craniotomy was removed that measured 14 by 8 cm. on its superior surface and ran down the entire depth of the falx to the corpus callosum.

CASE 3. W. R., a 19 year-old, unmarried man, was admitted to the Neurologic Service of the Boston City Hospital in December, 1936 because of convulsive seizures beginning 9 months previously. The maternal grandmother had had epilepsy, and the patient had had three severe injuries at 1, 7 and 12 years all to the left parietal region at least one of which had fractured the skull. At first the seizures consisted of severe pain in the right arm that spread to the right leg, lasting less than a minute followed by numbness, transient aphasia and generalized weakness. Later the seizures were accompanied by tonic movements of the right arm (chiefly extension) and shortly before entry the attacks began to be accompanied by loss of consciousness.

Physical examination on entry was entirely negative as were routine blood and urine examinations, the blood Hinton reaction, x-ray films of the skull and an air encephalogram by the lumbar route.

The patient was discharged on 2½ gr. (0.15 gm.) of phenobarbital daily, but his seizures grew more severe and frequent and in April, 1937, he was started on 4½ gr. (0.3 gm.) of Dilantin daily. This was later increased to 7½ gr. (0.5 gm.) daily. The seizures improved somewhat with this treatment but in September, 1937, he was readmitted to the hospital. This time there was some weakness of the right arm and deafness of the middle ear type on the left. Routine laboratory

examinations were again normal. Another air encephalogram showed normal filling of the lateral ventricles which were normal in size and position. The films were said to show a possible diffuse cortical atrophy on the right (sic).

The patient then went to another Boston hospital where a radical left mastoidectomy was done in November 1937, without relief of symptoms. In February, 1938, a craniotomy was performed there and the left parietal lobe was exposed. The left motor area was found to be atrophic. According to the operative note the pathology was so obvious that no attempt was made to stimulate the cortex. The patient was discharged on 3 to 4½ gr. (0.2 to 0.3 gm.) of phenobarbital daily and continued to have daily seizures.

The patient was readmitted to the Neurologic Service in August 1938. For the first time a right lower facial weakness was noted. Routine studies were normal, but lumbar puncture was not performed.

For the next 4 years the patient spent much of his time either in the Boston City Hospital, the Monson State Hospital or the Boston State Hospital. He exhibited progressive personality deterioration and continued to have frequent seizures despite anticonvulsant therapy. The seizures were usually of the type described above but generalized seizures of grand mal type also occurred and even on occasion seizures localized to the left arm. No changes were noted in the neurologic examination, and the right lower facial weakness persisted unchanged.

In November, 1942 the patient was admitted to the Boston Psychopathic Hospital because of aggressive behavior toward his family, urinary incontinence and failing memory. Physical examination revealed bilateral papilledema of 3 to 4 diopters and right lower facial weakness. Visual acuity was markedly reduced. On December 19, a craniotomy was performed immediately after a ventriculogram and an extremely large fibrillary astrocytoma that had practically replaced the left temporal lobe was removed.

SUMMARY AND CONCLUSIONS

The records are presented of 3 patients with convulsive seizures who had normal air encephalograms, seven, twenty and thirty months, respectively, after their first convulsions but who were subsequently proved to have brain tumors. All three tumors were astrocytomas, one in the left temporal lobe, one in the right motor area and one in the right frontal lobe.

Although brain tumors are among the rarer causes of convulsive seizures, such tumors may cause convulsive seizures without producing any demonstrable distortion of the ventricular system. Cerebral tumors are not apt to produce any change in the ventricular system unless they are large enough to produce focal neurologic signs or increased intracranial pressure, as evidenced by choking of the disks or increased cerebrospinal-fluid pressure on lumbar puncture. If in the absence of these it is decided that an air study is advisable, a negative report should not be accepted as conclusive proof that no tumor is present.

MEDICAL PROGRESS

CARDIOGENIC SHOCK*

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IN VIEW of the fact that inadequate cardiac output appears to be the most important direct cause of the clinical picture of shock, it is somewhat singular that in the majority of cases peripheral rather than central circulatory defects are at fault. It is also somewhat singular that wider recognition has not been given to the possibility that shock may result from sudden diminution of cardiac output due to factors inherent in the heart itself. It is generally known that the shock syndrome may arise in a variety of diseases affecting the central circulatory apparatus, but many clinicians feel the necessity of assuming the presence of peripheral vascular collapse in such cases. Even in traumatic shock, the possible importance of heart failure as a sustaining factor has recently received attention,¹ and physiologists have long recognized the importance of cardiac mechanisms in maintaining blood pressure and blood flow.

Clinicians have been accustomed to thinking of all types of shock as having a similar pathogenesis—namely, an insufficient effective circulating blood volume. This point of view has been fostered by the concept that all cases of shock can be attributed to a disproportion between the circulating blood volume and the size of the vascular bed. Atchley² first applied this criterion to both surgical and medical shock, and it has been subscribed to by Blalock³ and Moon.⁴ This definition has the appeal of conciseness and reasonableness, but it leaves out of account the possibility that simple redistribution of blood, with depletion of the arterial side, can occur, and that shock may appear in the absence of any significant reduction of blood volume or increase in the total vascular bed.

That shock can occur in the presence of high venous pressure and adequate filling pressure of the heart is evidenced by the fact that the condition is often seen terminally in patients with chronic congestive heart failure due to hypertension or aortic valvular disease.⁵ Since many clinicians depend on differentiating shock of peripheral origin from shock of central circulatory origin by means of the peripheral venous pressure, it remains to consider whether shock due solely to heart failure can occur in the absence of peripheral venous engorgement, and to inquire into the evidence for and against this possibility.

It is first necessary to review briefly some fundamental facts that must be kept in mind if confusion is to be avoided. It must be readily apparent that the state of the peripheral veins is dependent largely on arterial inflow, and that the reduced arterial flow to the superficial structures in shock results, other things being equal, in collapsed superficial veins. This applies in a somewhat lesser degree to the veins of the neck. Adequate filling of the heart, however, depends on the effective pressure in the auricles—that is, the height of auricular pressure above intrathoracic pressure—and not on pressure in the superficial veins. Right auricular pressure (referred to as atmospheric pressure) in traumatic shock⁶ has been measured and found to be low, but has apparently never been measured in cardiogenic shock. In some forms of the latter, however, the pressure in the femoral vein has been found to be significantly higher than that in the antecubital vein.⁵ Furthermore, the peripheral manifestations of shock are dependent on a diminished output of the left ventricle, the filling pressure of which cannot be gauged by pressure in the right auricle, and even less by pressure in the peripheral veins.

Another important question is whether or not additional blood can be accommodated on the venous side of the circulation without unduly distending any vein or significantly raising the pressure within it. There can be little doubt that in a normal person a venous reservoir exists in the form of unused channels, and that even the channels in use can accommodate more blood without demonstrable effects on the pressure within the veins. The rapid intravenous infusion of large amounts of fluids can be accomplished in normal persons with only a slight and fleeting rise in venous pressure. Obviously, the amount of additional blood that the venous system can accommodate depends on how well filled the venous system is to begin with, and this is a function of the volume of circulating blood. It has been shown by Gibson and Evans⁷ that the circulating blood volume is regularly increased in congestive heart failure, and that the increase begins with early loss of cardiac reserve and does not depend for its inception on marked congestive failure. It is apparent, therefore, that a cardiac event in a patient with a somewhat increased circulating blood volume may result in a combination of shock and congestive failure, whereas the same event occurring in a patient with a normal blood volume may result in a clinical picture of shock only.

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Support for this reasoning is commonly found in patients with acute myocardial infarction. When this event occurs in a patient previously suffering from congestive failure or loss of cardiac reserve, the striking circulatory alterations are likely to be predominantly manifested by an increase in the signs of congestion, whereas in patients who previously were well the signs of shock are likely to prevail.⁸

Further support for and discussion of the importance of the circulating blood volume, as well as other peripheral mechanisms, in determining the venous pressure in heart failure are offered by Starr, Jeffers and Meade.⁹ These investigators produced severe damage to the right ventricle of dogs, with resultant dilatation and failure of that chamber, without any significant increase in venous pressure. They were led to conclude that the results "give no support to the view that the peripheral venous congestion and the large increment of venous pressure so often associated with cardiac disease in man are caused directly and predominantly by failure of the right ventricle." In other words, heart failure seems to be less important in determining venous pressure than is blood volume or other unknown factors.

One further point in orientation needs to be considered. There are two clinical entities commonly producing the picture of shock that are due to central circulatory faults but not to failure of the heart as a pump. These are the rapid accumulation of fluid in the pericardial sac and massive pulmonary embolism. In both, striking engorgement of the neck veins is usually present and, since this may occur in previously normal patients with presumably normal blood volume, it has been taken to mean that sudden heart failure in previously well patients also results in engorgement of the peripheral veins. This line of reasoning contains an evident fallacy, for in pericardial effusion and in massive pulmonary embolism the pulmonary circuit is largely eliminated as a potential reservoir, and hence the entire amount of redistributed blood must be accommodated in the peripheral circuit instead of in both peripheral and pulmonary circuits, as in sudden failure of the left ventricle. That the pulmonary circuit is a reservoir of no mean magnitude is apparent from the fact that even patients with an increased total circulating blood volume may have no peripheral venous congestion despite a marked increase in pulmonary congestion due to failure of the left ventricle.

Since it is generally conceded that a variety of central circulatory faults may give rise to a combination of shock and congestive failure, this discussion will be mainly concerned with the forms of cardiogenic shock that may, at times, occur with normal or low peripheral venous pressure. If convincing evidence that the clinical picture of shock alone is due solely to cardiac factors can be brought forward, there seems to be no need to invoke peripheral mechanism to explain shock when it occurs in patients with obvious congestive heart failure.

TACHYCARDIA

Wiggers¹⁰ states that increasing the heart rate from 80 to 180 per minute results in a gradual diminution of output per beat with an increasing or steady output per minute, but that at rates above 180 the increasing number of beats per minute is unable to compensate for the diminishing output and, consequently, the total output falls. When the tachycardia is of ventricular origin, the critical rate is somewhat lower because of the abnormal excitation and less efficient contraction of the ventricles. These rates apply to normal hearts, and there is clinical evidence, as well as theoretical reasons, for believing that lower heart rates may significantly reduce cardiac output when there is underlying heart disease. Harrison¹¹ states that the collapse type of cardiac failure may occur with extreme tachycardia — usually over 170 per minute. Wolff¹² studied the effects of tachycardia in 125 patients and had the following to say about shock:

Although a fall in blood pressure was commonly observed during paroxysmal rapid heart action, in only 15 cases did collapse occur. . . . Four patients had normal hearts (1 with hyperthyroidism), 5 had mitral stenosis, 1 had free aortic insufficiency, 2 had angina pectoris, 2 had asymptomatic coronary-artery disease and 1 had recent cardiac infarction. . . . Four patients had congestive failure. . . . The ventricular rate was 200 per minute or more in 7, or almost half the cases, and was less than 150 in only 2.

Three factors appear to be significant in the genesis of vascular collapse: extremely rapid ventricular rates, embolism and aortic valvular disease. . . . When extremely rapid ventricular rates are attained, all other factors may be absent and the heart may be normal. . . . In the presence of aortic valvular disease vascular collapse may occur even though the ventricular rate is significantly under 150 per minute. . . . Occasionally, in elderly patients, vascular collapse may occur with only moderately rapid ventricular rates, even though other contributing factors are not evident.

Sturnick, Riseman and Sagall¹³ studied 21 patients with various types of ectopic tachycardia and found shock in 15. Dyspnea was usually, but not invariably, present, whereas congestive failure occurred only twice. Pulmonary edema was associated with the tachycardia in 4 cases. Only 1 patient in whom shock occurred, a sixty-five-year-old man, was thought to have no underlying heart disease.

Marshak¹⁴ reported a case of circulatory collapse associated with the onset of supraventricular tachycardia at a rate of 215 per minute in a young woman with an essentially normal heart. This occurred post partum, and associated blood loss or other factors may have played a part in the genesis of the vascular collapse.

A few cases of extremely rapid ventricular rates have been reported. These have been collected by Edeiken,¹⁵ who adds a case of his own. This occurred in a patient who was convalescing from acute myocardial infarction that had occurred twenty-four days previously. The onset of supraventricular tachycardia at a rate of 310 per minute resulted in vascular collapse without signs of congestive failure. In discussing other reported cases of extreme tachy-

cardia, Edeiken points out that although collapse or congestive failure may occur it is often surprising how little an occasional patient is incapacitated by ventricular rates as high as 300 or more.

In summary, it appears that tachycardia may produce the clinical picture of shock, in many cases without signs of congestive failure, but that it does not invariably do so. In patients with no underlying heart disease and with no other contributing factors present, shock does not occur at heart rates below 180, and probably but rarely at rates below 200. When underlying heart disease is present, rates well below 150 may produce shock. Since shock itself is commonly accompanied by heart rates of 150 or more, it becomes of some importance, in occasional cases, to determine whether the tachycardia is ectopic and whether underlying heart disease is present.

In view of the correlation of the presence of shock with the onset and offset of tachycardia, and the correlation of observed critical rates with expected critical rates, there appears to be no need to invoke mechanisms other than the cardiac one to explain the presence of diminished cardiac output with resultant shock.

MYOCARDIAL INFARCTION

Infarction of the heart is, of course, the cardiac accident most frequently associated with shock. Often there is clear-cut evidence of both shock and peripheral congestive heart failure, but many cases give clinical evidence of shock alone. Since the clinical findings in cases of shock associated with myocardial infarction are sometimes identical with those in traumatic shock, many clinicians have become accustomed to thinking of both as having a common cause. It is not to be inferred that this concept is universal, for Harrison¹¹ and many others have long held that shock in myocardial infarction is due to so-called "hypokinetic forward failure." Inasmuch as the therapeutic approach to this grave manifestation of infarction is necessarily guided by a correct understanding of its mechanism, it seems desirable to evaluate the present knowledge concerning it.

At the outset it should be emphasized that, save for neurogenic shock, none of the currently popular theories of traumatic shock can reasonably be applied to shock in myocardial infarction. Certainly, sufficient loss of plasma into the infarct to produce shock cannot well be imagined, and it seems unlikely that liberation of a histaminelike substance sufficient in amount to paralyze the systemic capillaries is of importance. The search for a toxic substance liberated by traumatized or ischemic tissue is periodically revived and has recently been investigated by Green.¹⁶ He was able to produce a shocklike picture in animals by the injection of an extract of skeletal muscle that proved on analysis to be barium adenosine triphosphate. Whether this

substance has anything to do with traumatic shock is still extremely doubtful, but in relation to muscle damage occurring in myocardial infarction it is pertinent to point out that Green found a lethal dose of the crude muscle extract to be roughly equivalent, in terms of fresh muscle, to one fifth the body weight. He also pointed out that the bulk of muscle that must be submitted to traumatic asphyxiation in order to produce severe shock in animals or man is very large. Unless cardiac muscle contains this toxic substance in a content many hundred times that of skeletal muscle, it is apparent that the concept of the liberation of such a substance to account for the shock in myocardial infarction must break down. Furthermore, such explanations leave unaccounted for the fact that the size of the infarct post mortem cannot always satisfactorily correlated with the presence or degree of shock during life.

Since a decrease in circulating blood volume is frequent, though not invariable, finding in traumatic shock, attention has naturally been directed toward this possibility in cases of shock associated with myocardial infarction. Fishberg, Hitzig and King¹⁷ investigated the circulating blood volume in patients with acute myocardial infarction and concluded that the shock was peripheral in origin. Critical analysis of their results, however, shows that significant reduction in blood volume occurred in only 1 case and that actually the average blood volume remained essentially unchanged. In the first edition of his book Fishberg¹⁸ held to the peripheral origin of shock in myocardial infarction, but in a later edition he reversed this opinion.⁸ The absence of a significant reduction in circulating blood volume has been confirmed in patients⁵ and repeatedly in experimental animals.¹⁹⁻²¹

A slight decrease in plasma volume and a slight hemoconcentration have been observed in patients with shock and myocardial infarction.^{5, 22} Stead and Ebert⁵ attributed this to loss of fluid through the pulmonary capillaries subsequent to pulmonary congestion. It is likely that, in some cases, excessive sweating or vomiting is an equally important factor for concentration of the blood proteins indicates loss of water rather than loss of serum or plasma. Though the degree of reduction in blood volume is insufficient alone to produce the picture of shock now apparent, it can be demonstrated beyond reasonable doubt.

Measurements of cardiac output in relation to shock in myocardial infarction have been hampered by the fact that the gravity of the illness in human beings has precluded the use of complicated and tiring procedures, and by the fact that shock is not invariably, or even frequently, produced by ligation of the coronary arteries in experimental animals^{19, 20, 23, 24} (a point of some importance that is further discussed below).

Grishman and Master²⁵ measured cardiac output in 5 patients with myocardial infarction by a phle-

ical method involving the determination of the velocity of the pulse wave. None of these patients were in shock, yet their cardiac outputs were significantly diminished. It seems reasonable to suppose that the cardiac output would be even more drastically reduced in the presence of shock. Starr and Wood²⁶ also computed the cardiac output — by means of the ballistocardiograph — in patients with acute myocardial infarction. They, too, found a significant reduction in cardiac output but, strangely enough, severe cases — including those with shock — showed, on the average, less reduction than those with signs of a mild illness. In correlating blood-pressure changes with changes in cardiac output, they state: "This reduction [in blood pressure] did not always run parallel to the diminution of cardiac output, and so was not the result of change in the latter. It should be considered another adaptive mechanism." In view of the suspicion, recognized by Starr himself, that the form and magnitude of the ballistocardiographic waves may be determined by factors other than cardiac output alone, their conclusions cannot be accepted as established. Indeed, it has been shown that, in cases of shock, the ballistocardiogram may give figures for cardiac output that are as high as 75 per cent greater than those obtained by simultaneous determinations made by the direct Fick principle, whereas the agreement in more normal subjects is closer.⁶

Gross, Mendlowitz and Schauer^{19, 20, 22} found that the significant hemodynamic changes occurring in experimental coronary occlusion were a decrease in cardiac output and an increase in circulation time. The blood pressure did not fall significantly, a finding noted by others studying experimental coronary occlusion.²¹ Mendlowitz, Schauer and Gross²¹ also studied the effects of ligation of the coronary arteries in denervated hearts. In such preparations the decrease in blood pressure was more striking than was that in animals with intact nervous pathways. The authors attributed this to the fact that some of the nervous pathways for compensatory vasoconstriction were interrupted. Since the carotid sinuses were not denervated, their conclusions must be accepted with reservations. Inasmuch as the heart itself was completely denervated, however, their results did indicate that reflexes from the heart were not directly responsible for the decline in cardiac output or blood pressure.

Stead and Ebert⁵ studied 6 patients with acute myocardial infarction and shock. In 3 of these the circulation time was moderately to markedly prolonged, and all showed x-ray evidence of pulmonary congestion. Massie and Miller²⁷ found x-ray evidence of pulmonary congestion in 12 of 16 patients with acute myocardial infarction, although rales were heard in only 7 patients.

In summary, it appears that the shock syndrome in myocardial infarction cannot be attributed to a decrease in venous return, for, in addition to the considerable number of patients who show actual peripheral venous congestion combined with shock, there is evidence, in the form of prolonged circulation time and pulmonary congestion in many cases, that pulmonary venous and left auricular pressures are high. Since the manifestations of shock are dependent on the reduced output of the left ventricle, it is obvious that the left auricular pressure is of greater significance than is the pressure in the peripheral veins. The evidence indicates, therefore, that the venous return to the left ventricle is more than adequate and that the fall in cardiac output with resultant shock cannot be attributed to the mechanisms that are thought to be important in traumatic shock.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

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CASE 30081

PRESENTATION OF CASE

A thirty-nine-year-old housewife entered the hospital because a left thoracotomy wound had failed to heal in the course of fifteen months.

The patient had enjoyed good health until seventeen months before admission, at which time she suffered an attack of pleurisy followed by pneumonia and empyema. She was admitted to a community hospital where, two months after the onset of her illness, a thoracotomy with resection of a portion of the left tenth rib was performed. One of eleven sputum samples examined was reported positive for tubercle bacilli and she was accordingly transferred to a sanatorium, where, during a stay of three months, numerous sputum and gastric examinations failed to reveal tubercle bacilli by smear or by guinea-pig inoculation. During her stay she lost 19 pounds in weight. On one occasion, when her wound was irrigated, she claimed to have expelled some of the irrigating fluid from her mouth. At home, the wound continued to drain intermittently and was associated with a sense of pressure on the left side and back, increasing on urination or defecation. The material discharged varied in color from red and yellow to water-clear; its consistence varied from thick to thin. In the intervals when drainage ceased she developed a cough, which was productive of reddish or yellow foul-tasting sputum. The temperature varied from normal to 104°F., averaging 99. Shaking chills occurred about every six weeks. She had profuse night and day sweats and, for three months prior to admission, dyspnea on exertion. She vomited frequently, especially when trying to work and had lost 50 pounds in the course of her illness. For the week prior to admission, the sense of pressure in the left side developed into a sharp continuous knifelike pain involving the side and back of the left chest and the left flank, radiating down the lateral aspect of the left leg to the ankle. Empirin Compound afforded some relief. She also had burning on urination, but no frequency or hematuria. The menses had been irregular throughout the illness.

Physical examination revealed a pale, weak and markedly emaciated patient in pain. Small tender

*On leave of absence.

nodes were palpable in the left axilla, left groin and both anterior cervical regions. There was diminished expansion of the left chest. A sinus-tract opening was present in the ninth left intercostal space the posterior axillary line. From this point, a tend visible and palpable mass extended downward on the left flank to about the level of the crest of the ilium. The heart sounds were regular and rapid with a crescendo, snapping first sound. The blood pressure was 110 systolic, 55 diastolic. The left leg was held in flexion at the thigh (45°) and knee (90°). Edema of the ankles and feet was present, being greater on the left. Pelvic examination revealed exquisite tenderness in the left vaginal vault, and a mass was palpable in this area on rectal examination. There were numerous external hemorrhoids.

Examination of the blood revealed a red-cell count of 3,500,000, with 60 per cent hemoglobin. The white-cell count was 24,000, with 88 per cent neutrophils. The urine showed adequate concentration with a specific gravity of 1.020, a + test for albumin and 4 or 5 white blood cells per high-power field. The stools were normal. The serum nonprotein nitrogen, sodium and cholesterol were within normal limits.

X-ray examination showed irregular areas of increased density obscuring the lateral chest wall. A defect was seen in the first portion of the left tenth rib, and from this defect a soft-tissue swelling extended down into the left flank. The lumbar spine appeared normal. Lipiodol injected into the first rib revealed a communication with a large cavity apparently reaching almost to the midline, displacing the stomach, and probably the colon, medially and extending downward to a point slightly below the crest of the ilium. The lipiodol moved freely within this cavity, and some of it apparently entered the small intestine. On a film after injection, opaque material was seen in the right upper quadrant. A barium enema revealed ptosis of the entire colon, which appeared normal except for evidence of extrinsic pressure on the descending portion. There was no evidence of communication with the abscess cavity. Thin barium injected into the fistulous opening in the chest wall entered a mass of fingered cavity seen to communicate with the small bowel. Some minutes later barium was seen in the stomach, although no direct communication was observed. Later, after a barium meal, no barium was observed to pass from the stomach into the sinus tract, which appeared to be in close association with the upper lateral wall of the body of the stomach. The barium passed into the duodenum and jejunum, the latter appearing to be several centimeters below the level of the sinus tract. An intravenous pyelogram revealed incomplete outlining of the left renal pelvis, with moderate dilatation and blunting of the calyces. There appeared to be a small pressure defect over the central portion, with incomplete filling of the middle calyces. A gastroscopy revealed a superficial

gastritis but no positive evidence of a fistulous opening into the stomach. A catheter passed into the chest sinus for a distance of 12 to 15 cm. did not enter the stomach.

The temperature ranged between 97 and 103°F.

The patient received several blood transfusions, one of which was followed by a mild reaction. On the tenth hospital day, the flank abscess was incised and drained. Thick, green, foul-smelling pus was encountered. The abscess cavity was observed to lead up under the diaphragm, toward the fundus of the stomach and splenic flexure and down posteriorly to the tip of the spleen and along the belly of the psoas muscle. Cultures of abscess pus and of material drained from the chest sinus revealed *Staphylococcus aureus*, *Staph. albus*, a nonhemolytic streptococcus, *Bacillus pyocyaneus*, fusiform bacilli and a few colonies of colon bacilli; no fungi grew on Sabouraud's medium. Of several guinea pigs inoculated with this material one was negative, the others dying too soon for a diagnosis to be made.

The wound continued to drain profusely. In spite of numerous transfusions, a stubborn anemia persisted, the red-cell count ranging between 3,000,000 and 3,500,000. The hematocrit varied between 30 and 40 per cent. The white-cell count averaged 17,000, with 71 per cent neutrophils. Several urine examinations revealed large numbers of pus cells. The prothrombin time was persistently prolonged, varying from 25 minutes (normal, 16 minutes) to 37 minutes (normal, 20 minutes). The blood total protein ranged between 4.8 and 6.6 gm. per 100 cc., with an albumin-globulin ratio of 1.0 on one occasion. A bromsulphalein test was negative. A Congo red test showed only 15 per cent dye absorption after one hour.

Because of the stubborn anemia and the evidences of nutritional deficiency the patient was given large doses of vitamins and liver extract parenterally, as well as considerable amounts of adrenocortical extract, in an effort to improve her condition. She was also given large doses of vitamin K (Hykinone).

On the thirty-first hospital day, the flank incision was again explored and the communication of the abscess cavity with the chest sinus was laid open. A necrotic mass presenting itself in the wound was biopsied and was reported as acute and chronic pyelonephritis and perinephritis. On the day following operation a catheterized urine specimen showed gross hematuria, but the urine later contained only 2 or 3 red cells per high-power field, as well as 15 to 20 white cells. Urine culture was positive for colon bacilli on this occasion, as well as for *B. pyocyaneus*, *Staph. albus*, *Clostridium welchii* and fusiform bacilli. An abdominal paracentesis yielded 1700 cc. of straw-colored fluid, which was negative on culture; it had a specific gravity of 1.010 and was negative for acid-fast bacilli and tumor cells.

On the thirty-eighth hospital day, the patient had to be placed on tube feeding because of persistent

vomiting. She continued to vomit, however, and expired two days later.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD H. SWEET: The fact that the thoracotomy wound failed to heal is of interest, since such a wound usually heals unless there is some residual disease.

The attack of pleurisy followed by pneumonia and empyema is another curious thing in this history. So-called "primary pleurisy" is usually caused by the tubercle bacillus. I suppose theoretically tuberculosis exists in the lung and then spreads into the pleural cavity, but ordinarily, tuberculous pneumonia does not follow pleurisy or empyema. The pleurisy follows the pneumonia. So I believe there is something peculiar about the chest situation in this case, and I doubt whether the chest lesion was the primary one. It seems to me that it probably was secondary to something below the diaphragm.

"... numerous sputum and gastric examinations failed to reveal tubercle bacilli by smear or by guinea-pig inoculation." I should like to interpolate that in my opinion the patient did not have tuberculosis because few positive cases are missed in a sanatorium. We have occasionally seen patients in whom supposed acid-fast organisms were found and who were sent to a sanatorium, where no evidence of tuberculosis could be found. Such patients eventually return, and the correct diagnosis of a nontuberculous lesion is made later.

"On one occasion, when the wound was irrigated, she claimed to have expelled some of the irrigating fluid from her mouth." What does that mean? If she had a fistula between the empyema cavity and a bronchus she would not speak of expelling the fluid; she would have coughed and brought it up. Therefore I suggest that the communication must have been below the diaphragm or through the diaphragm into a loop of bowel or into the stomach. Of course one cannot argue too much from the way the record is worded; but if the wording is correct, she did not have a bronchopleural fistula. That raises the question whether she might not have had a lung abscess. Of course, a lung abscess that had perforated, with a resultant empyema, might produce a bronchopleural fistula after drainage of the empyema. But there is no mention of the fact that the pus was foul smelling early in the course of the disease.

"Shaking chills occurred about every six weeks." I do not know of any disease with such periodicity. That does not mean much to me.

Night sweats may go with tuberculosis of the lung, but they may accompany any type of sepsis. She had a right to have the dyspnea on exertion. Furthermore, she appeared to have been sick enough to lose 50 pounds in weight, and I do not believe to assume that she had tuberculosis.

This is probably not a prime cause she had no hematuria

enough sepsis to account for the tender lymph nodes. The tender mass and the pain make one think that she had an abscess in the flank, and as the case develops, the whole question centers on the abscess in that region. She has psoas spasm, which indicates that it was a deep abscess extending along the course of the psoas muscle. Pelvic examination confirmed that impression because it revealed "exquisite tenderness in the left vaginal vault." In other words this abscess had burrowed its way down through the flank and into the pelvis, which is not at all uncommon. The diagnosis, I think, will be greatly influenced by the x-ray films.

There is reasonably good evidence, both clinically and by x-ray, of perinephric abscess, or possibly subphrenic abscess. I am inclined to think it was the latter.

"On a film after injection, opaque material was seen in the right upper quadrant." It does not say whether that was in a hollow viscus or in the peritoneal cavity. If it was in the peritoneal cavity, we must be dealing with a subdiaphragmatic abscess.

"Later, after a barium meal, no barium was observed to pass from the stomach into the sinus tract, which appeared to be in close association with the upper lateral wall of the body of the stomach." That is exactly where it would be if it were a subdiaphragmatic abscess. It appears that we have evidence of a fistula communicating with the jejunum but not with the stomach or with the colon.

There is no mention of a tumor or of an ulcer on gastroscopic examination.

DR. LAURENCE L. ROBBINS: In the chest films there appears to be something in the region of the left costophrenic angle that I think could be all pleural. There is nothing definite within the lung. These films show that the sinus tract passes anteriorly and divides into many small branches. I assume that this is the material that went into the small bowel, and on one of the large films we can see that it has appeared in the stomach. The one thing that is impressive is that there is no evidence of a visible outline of the left kidney, and the psoas shadow is obliterated. The stomach, except for displacement, is not abnormal.

DR. SWEET: The sinus leads into the abdomen, however.

DR. ROBBINS: It goes a considerable distance farther forward than one would expect to find the kidney. It extends to a plane anterior to the spine.

DR. SWEET: Dr. Robbins is anticipating me. I was going to say that this could not have been a perinephric abscess.

It is rather interesting to speculate why adrenocortical extract was given. Because of the fistulous tract I wondered about diarrhea, but there is no mention of it. She had some disease that depleted her.

DR. FRANCIS D. MOORE: The patient did not have diarrhea.

DR. SWEET: This patient, with months of observation under medical care, had several attempts made to prove or disprove the diagnosis of tuberculosis. I believe it is reasonable to exclude such a diagnosis. As I have said, the sanatoriums do not miss that diagnosis very often, and one guinea-pig inoculation in this hospital, after the lapse of a proper length of time, showed no evidence of it. Therefore we must come down to a consideration of the etiology of a large subdiaphragmatic or perhaps perinephric abscess.

Perforation of a perinephric abscess into the abdominal cavity is a most unusual occurrence. I do not recall seeing it. Dr. Colby, who has seen many more perinephric abscesses than I have, tells me that he has seen only one that ruptured into the abdomen. We must always keep the two things entirely separate. Therefore, if my reasoning so far is correct, we are dealing with an abscess in the left upper quadrant of the abdomen, a subdiaphragmatic abscess that has done a number of things—namely, perforated through the diaphragm to cause empyema, extended into the pelvis and produced pyelonephritis. I have perhaps excluded the lung and pleural cavity as the source of all this mischief a little too rapidly, but there is no mention of anything that makes me think she had disease in the lung. The x-ray films do not show any residuum of disease in the lung, and the story suggests that she had something going through the diaphragm, and as we see later, she had a fistula. An empyema rarely perforates into the peritoneal cavity; on the other hand, a subdiaphragmatic abscess frequently perforates into the pleural cavity. Thus, the current is the other way. With these apologies, I shall exclude the chest as the source of the disease.

If there was a subphrenic abscess, either intra-peritoneal or abdominal, where did it come from? A subphrenic abscess always arises from some septic focus within the abdomen. The commonest cause is a perforated viscus, such as a ruptured gall bladder, appendix or diverticulum, or through a malignant tumor in a hollow viscus. Occasionally a liver abscess perforates and causes a subphrenic accumulation of pus, but that is unusual. Then there is the occasional case in which a picture like this can be explained entirely by acute pancreatitis. Some patients with necrosis of the pancreas develop large accumulations of pus, usually in the left part of the upper abdomen, which ulcerate into the viscera, perforate the diaphragm or gravitate down along the psoas muscle or even into the pelvis. In such cases, we sometimes drain the pancreatitis through the inguinal region because the abscess has presented as a bubo in the groin, having gone all the way down by the retroperitoneal route.

There is one other condition that I have not mentioned because it did not seem to fit in very well. Could the trouble have started from an infection in the spine—an osteomyelitis? When I originally

thought of tuberculosis I wondered if it might have been a tuberculous lesion starting in the spine. The x-ray films do not suggest a spinal lesion, and the patient did not behave like one with osteomyelitis of the spine.

I should conclude my discussion by deciding whether this subdiaphragmatic abscess arose from a ruptured viscus or from an acute pancreatitis, but I cannot say which it was.

DR. CASTLEMAN: The field is still wide open.

DR. FLETCHER H. COLBY: The possibility of perinephric abscess is naturally good. My experi-

whole region, including the kidney. Later on, as we got the x-ray films, it seemed that the viscus entered was not the splenic flexure but either the stomach or the small bowel. We continued working on that assumption—accidental perforation through the low thoracotomy site, which had allowed sepsis to be introduced into the abdomen from the gastrointestinal tract.

The patient was given adrenocortical extract because, along with the chronic pyogenic infection, she had evidence of adrenal insufficiency. The blood sodium was 120 millicquiv. per liter, and the 17-

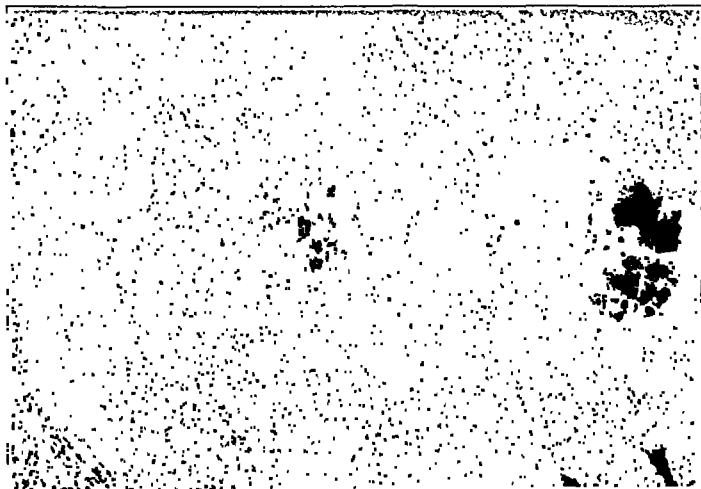


FIGURE 1. Actinomycotic Clumps in an Abscess of the Liver.

ence with a perinephric abscess that involves the peritoneal cavity is rare. In the only case that I can remember, the patient died very quickly. Whether it can involve the intraperitoneal contents without causing peritonitis, such as this individual had, I do not know.

DR. MOORE: When the patient came in on the surgical service she presented the enigma that Dr. Sweet has described: she had supradiaphragmatic and subdiaphragmatic sepsis, and the problems were how it got from one place to the other, and what was the origin. Our reasoning was guided by one fact that is not stressed in the abstract of the history. The original thoracotomy wound was at the level of the tenth rib in the midaxilla; this was too low for the drainage of an empyema, and was so low that one could with great ease penetrate through the diaphragm and perforate a subdiaphragmatic viscus. We thought that this accident had occurred, possibly with perforation of the splenic flexure, and that this gastrointestinal sepsis had swamped the

ketosteroids were low. We gave the extract in an effort to restore this endocrine imbalance.

CLINICAL DIAGNOSES

Subdiaphragmatic abscess, probably originating from perforation of intestine.
Pylonephritis.

DR. SWEET'S DIAGNOSIS

Subdiaphragmatic abscess, originating from perforated viscus or acute pancreatitis.

ANATOMICAL DIAGNOSES

Actinomycosis of left retroperitoneal and retropleural spaces, left kidney and liver.
Perforation of splenic flexure of colon.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy on this patient showed what was to be expected—a large abscess in the left retropleural and retroperitoneal regions

extending from about the level of the fourth rib through the diaphragm down to the level of the head of the femur. It did communicate with the splenic flexure, and not with the small bowel. There was a definite fistulous tract between the abscess and the splenic flexure. The kidney on that side was practically destroyed by this abscess, and we were unable to find the left adrenal gland. We also noticed that the liver was full of abscesses of varying sizes, which contained yellowish-green material. We made a diagnosis of abscess (type undetermined), with abscesses of the liver, and thought that the patient had a terminal septicemia.

Microscopic examination of the wall of the abscess, as well as of the abscesses within the liver, showed large numbers of actinomycetes. Hence, there was definite actinomycotic infection of the kidney, retroperitoneal space and the lower part of the left pleural cavity. The left lower lobe was completely collapsed, and we were unable to find any evidence of infection within the lung itself. Until Dr. Moore just said what he did about the rib resection, I was at a loss to explain how the actinomycotic infection arose. If it had arisen from the lung, as it often does, it would seem a little far fetched to believe that the infection within the lung disappeared and that the infection below the diaphragm continued. Also, a primary actinomycotic infection of the kidney is extremely rare; I think that it has been reported but it is ordinarily a secondary infection. I now believe that the perforation of the splenic flexure at the time of the rib resection released the organisms, which we know are often present in the normal colon. After the infection was well established, the portal vein was invaded by the organisms and a diffuse hepatic infection resulted.

DR. MOORE: Have you any explanation why the biopsy showed no actinomycetes?

DR. CASTLEMAN: We reviewed this slide after the autopsy and still could find no evidence of actinomycotic infection.

DR. MOORE: I might also mention that Dr. Cora Owen, of the Surgical Bacteriological Laboratory, who is interested in the study of actinomycoses, was unable to culture them. There was a large quantity of material to work with, and it was planted on all kinds of mediums at varying oxygen tensions, but no organism grew out.

DR. CASTLEMAN: The liver abscesses were full of actinomycotic clumps (Fig. 1). It is the best case that we have seen since the days of Dr. J. Homer Wright.

CASE 30082

PRESENTATION OF CASE

A sixty-five-year-old man, a retired bank clerk, was admitted to the hospital with anorexia and epigastric pain.

About three months before admission the patient began to experience anorexia, associated with gnawing pain in the epigastrium and region of the umbilicus. The pain was worse early in the morning and from a half to two hours after meals, but was not relieved by food. It was associated with deep pain in the back, at about the level of the seventh to the ninth dorsal vertebra, and with increasing weakness and malaise. For several weeks prior to admission he had complained of frequent attacks of nausea after meals, aggravated by the ingestion of greasy foods. He also stated that his bowel movements, which had occurred regularly twice daily, altered to once a day. Twelve days before entrance into the hospital his bowel movements ceased entirely for a period of six days, during which time only flatus was passed, but a dose of castor oil brought relief. Two days before admission, after taking a drink of whisky, he had an episode of bilious vomiting. Over a period of nine months the patient had lost 40 pounds of weight, half of this in the two or three months prior to admission. He had had an early morning cough associated with a small amount of expectoration for as long as he could remember, but he first noted wheezing about six months before entry. The wheezing was most noticeable when he was lying down, and diminished when he sat up. In the two months before admission, he had also noticed that he could walk only short distances without becoming short of breath, and in addition, his ankles were somewhat swollen. No orthopnea was present.

At the age of ten, the patient had rheumatic fever and was confined to bed for three weeks. At about the age of twenty-five, he had a chancre of the penis associated with a positive Wassermann test, for which he was treated over a period of two years. At about the same time he had gonorrhea. Twenty years before admission he had an attack of pain in the right upper quadrant, associated with nausea and vomiting, and following this a cholecystectomy and appendectomy were performed. Five years before admission he had an attack of abdominal pain that was diagnosed as being due to intestinal obstruction. He was admitted to a hospital but was treated nonsurgically. The patient was a moderate smoker, but drank heavily, consuming about a pint of whisky daily until he ceased working several years before admission. Since that time he usually drank seven or eight glasses of beer daily. During the year prior to admission he developed pain in the shoulders and hips, which was aggravated by cold weather and caused some difficulty in walking. His mother had died of cancer of the liver.

Physical examination revealed a weak, poorly nourished man. The skin was rough to touch, and there was exfoliation over the shins. Circumscribed areas of pigmentation and exfoliation were present in the axillary and inguinal regions. Numerous telangiectases were present on the face. On the

buccal mucosa were numerous soft, blue, vascular nodules, some of which were lobulated. The scleras appeared icteric. The lungs revealed diffuse inspiratory bronchial rhonchi, and an area of dullness to percussion was present about a handbreadth below the right axilla, extending posteriorly and unassociated with changes in breath sounds. In the epigastrium a nodular mass could be felt extending seven fingerbreadths below the xiphoid process and to the left midclavicular line; the edge was blunted and tender. In the right midclavicular line the liver edge was palpable two and a half fingerbreadths below the costal margin. There was some tenderness, and a suggestion of a mass, in the left upper quadrant. The extremities revealed a fine muscular tremor, tortuous brachial arteries, cyanotic and brittle nails, and redness and mottling of the palms. The knee jerks were active, and the Babinski sign was positive bilaterally.

The blood pressure was 150 systolic, 110 diastolic. The temperature was 98°F., the pulse 88, and the respirations 20.

Examination of the blood showed a red-cell count of 3,920,000, with a hemoglobin of 15 gm. The white-cell count was 8000, with 78 per cent neutrophils. The urine was negative. The stools were loose, brown and guaiac negative. The van den Bergh was 1.6 mg. direct and 2.5 mg. indirect. The blood phosphatase was 10.5 Bodansky units per 100 cc. The blood nonprotein nitrogen, the carbon dioxide combining power and the chloride were within normal limits. The blood protein was 6.8 gm. per 100 cc., with an albumin-globulin ratio of 0.8. The cholesterol was 225 mg. per 100 cc. A cephalin flocculation test was ++ after twenty-four and forty-eight hours. A blood Hinton test was negative.

A gastrointestinal series showed displacement of the stomach to the left and anteriorly by a mass in the region of the liver, and a pressure defect was present on the lesser curvature. A barium enema revealed several diverticulums in the proximal portion of the sigmoid, but was not otherwise unusual. A roentgenogram of the chest showed an area of increased density in the left lower chest, blunting of the left costophrenic angle and a prominent left hilus.

The patient was given a high vitamin diet and intravenous fluids but failed to respond; he gradually became stuporous and comatose and expired quietly on the twentieth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. FRIEDRICH W. KLEMPERER: This patient's chief complaint points toward involvement of the digestive system, and physical as well as x-ray examination demonstrated a mass that in all probability was the left lobe of the liver. There are a number of possibilities to explain the enlargement of the liver in this patient. He had had syphilis twenty-five years before admission and he could

have had a syphilitic cirrhosis. We know, however, that he had immediate and apparently adequate treatment and his Hinton test was negative. Neither of these rules out late syphilis but taken together, as well as the fact that involvement of the liver in late syphilis is quite rare, they make this diagnosis highly improbable.

The patient was also an alcoholic, and portal cirrhosis of the liver is therefore a good possibility. Several statements in the record, however, are against cirrhosis as the chief source of his trouble. These are the extremely rapid progression of the symptoms, the emaciation and presumably the increase in the size of the tumor, the absence of ascites or evidence of collateral circulation and the absence of splenomegaly. All these facts, however, could be easily explained if the patient had developed a hepatoma on the basis of an early cirrhosis. This must be weighed against the probability of metastatic malignancy to the liver.

What is the evidence we have for a primary lesion elsewhere? The patient had had an attack of so-called "intestinal obstruction" five years before admission. The lack of progression and medical cure definitely rule out the presence of cancer of the bowel at that time. We know that he had diverticulosis at the time of admission, and his previous attack of abdominal pain can logically be explained as having been due to diverticulitis. The recent change in bowel habits seems unlike that usually seen in obstruction due to malignancy and can easily be explained as secondary to the liver disease. The stools were guaiac negative. I see no reason why we should doubt the x-ray evidence that there was no lesion in the large bowel. Similarly we have no evidence that leads us to place the lesion higher in the intestinal tract. Primary carcinoma of the pancreas must always be thought of because it so easily escapes clinical detection. This is an appealing diagnosis because it would explain the character and distribution of the patient's pain near the umbilicus and in the back. Such a lesion would have to have been located in or near the tail of the pancreas, because carcinoma of the head would have led to progressive and severe jaundice. Although primary carcinoma of the pancreas is a distinct possibility, I am going to discard it in favor of a primary lesion in the lungs.

It should be remembered that nine months before admission — that is, six months before the onset of abdominal symptoms — he began to lose weight. Definite respiratory symptoms also preceded the abdominal symptoms by three months. The patient complained of wheezing respirations and dyspnea. These symptoms, particularly in the absence of orthopnea, are highly characteristic of lung tumor. They are most frequently seen in bronchiogenic carcinoma but can also occur in metastatic malignancy. For two reasons I am inclined to believe that the pulmonary lesion was primary rather than

metastatic from a primary lesion in the liver or pancreas. The first is the fact that the pulmonary symptoms preceded the abdominal ones by several months, and the second, that Dr. Robbins tells me that the x-ray changes in the chest are unlike those seen in metastatic malignancy. The age of the patient and the clinical course seem consistent with the diagnosis of bronchiogenic carcinoma with metastases to the liver. I see no evidence in the record to make one consider seriously the possibility of lymphoma or even sarcoma.

There are several points in the record that require comment. The patient had skin lesions. I interpret these as having been due to nicotinic acid deficiency. The telangiectases do not seem to bear any relation to the patient's illness. Their description does not indicate that they were the spider angiomas sometimes seen in cirrhosis of the liver. The patient had joint pain. The multiplicity and symmetry of involvement are against metastatic disease. There are not enough data to differentiate degenerative joint disease and rheumatoid arthritis. The latter seems somewhat more likely in view of the joint disease that the patient had during childhood, then diagnosed as rheumatic fever. The laboratory data indicate some parenchymal involvement of the liver. This may mean that the patient had a cirrhosis of the liver in addition to metastatic disease, but it is known that extensive malignancy can produce these changes. The immediate cause of death was probably general malnutrition but possibly liver failure.

CLINICAL DIAGNOSIS

Metastatic carcinoma of liver (?source).

DR. KLEMPERER'S DIAGNOSIS

Bronchiogenic carcinoma, with metastases to liver.

ANATOMICAL DIAGNOSIS

Oat-cell carcinoma of lung, with metastases to regional lymph nodes, liver, pericardium, right adrenal gland and rib.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The post-mortem examination disclosed a primary tumor in the lower or lingula branch of the left upper-lobe bronchus, with almost complete obstruction. The tumor involved about 4 cm. of the bronchus and had extended into the surrounding parenchyma. The carinal lymph nodes were involved and were matted together to form a 6-cm. mass. The lung distal to the tumor showed secondary bronchiectasis. The liver weighed 3000 gm., and about three fourths of it was replaced by metastatic cancer. Other metastases were present in the parietal pericardium, the right adrenal gland and one of the ribs. Microscopically the carcinoma is of the oat-cell type. This is the type that is usually located near the hilus and grows very rapidly.

We found no evidence of syphilis.

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A MARCH OF MERCY

As Red Cross Month comes around, the Nation is reminded once more of the American Red Cross and its stupendous task of relieving human suffering. The organization is national only in name, for its fighting fronts have been extended to every corner of the globe.

The immediate need is for blood donors and nurses. During 1944 the Red Cross must supply some 5,000,000 blood donations for military and civilian needs, and each month 2500 nurses must be received for the Army and Navy. In addition the large corps of field directors, hospital workers and other trained personnel must be kept at fighting strength, and where necessary increased. An im-

portant part of the war work is the preservation of morale in the armed forces by maintaining contacts between soldiers and sailors and their families, especially when domestic troubles arise. It goes without saying that, as ever, the American Red Cross must be ready to cope with disasters and epidemics at home, as well as with the endless needs of a nation at war.

All the activities of this vast organization are financed by voluntary gifts and contributions. During March, designated by President Roosevelt as Red Cross Month — in both senses a March of Mercy — the American Red Cross must raise a war fund of unprecedented size to meet unprecedented needs. More than ever, a generous answer to its appeal will be a gesture of patriotism and a sign of love for mankind.

PENICILLIN IN WOUNDS

ALTHOUGH only a small number of physicians in this country have had an opportunity to use penicillin, it is now fairly well established that this agent is highly effective in the treatment of many types of bacterial infection. It has already proved to be a lifesaving measure, surpassing the sulfonamide drugs in effectiveness under certain conditions. This has been particularly true in certain cases of staphylococcal septicemia and of meningitis. It is also highly effective in the treatment of infections with strains of gonococcus and pneumococcus that are resistant to sulfonamide therapy, and it may eventually prove to be the most effective agent in the treatment of syphilis and perhaps of other infectious diseases. The results of studies of the use of penicillin in surgical conditions in the past indicate that large doses are needed in the successful treatment of well-established wound infections, frequent doses of the drug being given parenterally and locally for long periods. In view of the limited supply now available, only a small percentage of established wound infections can receive the benefits of treatment with this agent.

The question naturally arises whether the early use of penicillin locally in fresh wounds wards off serious infections. Should it be possible thus to prevent infection in fresh wounds of soft tissue and

in compound fractures, obviously a large number of patients would be spared prolonged and severe illness and many limbs and even lives would thus be saved. Furthermore, this might readily be accomplished with a relatively small amount of penicillin and could, therefore, be made soon available for use in large numbers of battle wounds in the present conflict.

To investigate this aspect of the management of wounds, two eminent British investigators, Professor H. W. Florey, who has been intimately associated with the developments in penicillin therapy, and Brigadier Hugh Cairns, a leading surgeon, set out to make an intensive but brief study of the treatment of wound sepsis in North Africa. They had the collaboration of many medical officers and investigators. A detailed preliminary report of their findings was made to the British War Office and to Medical Research Council, and an abstract of this report has been published.¹ An additional study in Britain of the value of penicillin in infected burns and surface wounds is reported in the same issue of the *Lancet* by Flight Lieutenant D. C. Bodenham.²

In the investigations in the Mediterranean area local applications were made in four forms. The first was a solution of the calcium salt in distilled water or saline (250 to 500 units per cubic centimeter), and the second, a cream with lanette wax (250 units per gram). The latter holds penicillin in contact with tissues longer than is possible with a water solution and is itself soluble in water. The third form was crude, dried calcium penicillin applied directly to the infected surface, the penicillin dissolving in the fluid present. This method was thought to be unnecessarily wasteful because the powder is difficult to spread thinly over a large wound; furthermore, the powder, as such, is irritating when used locally. Finally, the powder, diluted with a sulfonamide, was insufflated on the infected area with a blower — sulfanilamide was used by Florey and Cairns, and sulfathiazole by Bodenham. The mixture contained 500 to 5000 units of penicillin per gram. In many cases it was necessary to supplement local treatment with parenteral therapy in large amounts.

A small number of chronic septic wounds of three to four months' standing were treated at Algiers.

The results in these cases were not encouraging, and it was concluded that treatment of long-standing septic compound fractures would require large amounts of penicillin, which might be more profitably used in more recent wounds.

Early closure of soft-tissue wounds was carried out in 171 cases by ten surgeons at five general hospitals at Tripoli and Soussé. Most of these wounds were three to twelve days old when closed; they were usually infected, and some were actually purulent. As experience and confidence grew, it was found possible to close almost all wounds except those in which the missile had produced gross destruction of skin. The medical officers who carried out the treatment were most enthusiastic about the results of closure of recent fresh wounds, and one of them remarked that with penicillin the obstacle of infection had been practically overcome.

In the treatment of recent compound fractures the aim was to prevent chronic infection and to convert them as soon as possible into closed fractures by suturing the wound. The cases available had been temporarily immobilized in the forward area and were five to fourteen days old on arrival at the base hospital. In this group, intramuscular injections or injections by continuous drip of penicillin were used, up to a total of 500,000 units, in addition to the local therapy. The wounds were completely sutured, except for a few in which this was mechanically impossible. In summing up the results obtained in recent fractures it was thought that too much had been attempted in the way of wound closure. Thus, in a comminuted fracture, it seemed better to leave potential drainage to the exterior for the first week or ten days. It was also thought that the dosage in the compound fractures of the tibia and femur was too small — in other words, that total of 700,000 to 1,000,000 units should be given over a period of seven to ten days, although this might prove unnecessary in patients who had received penicillin in the forward area.

Only a small number of cases of gas gangrene were treated. Although there was some evidence for a favorable effect, the final results were not encouraging: toxemia was not counteracted, and it was thought that fulminating cases could not be saved by penicillin alone. On the other hand, it was

stated that penicillin might be expected to play an important role in prevention.

The study of the use of penicillin in head wounds was chiefly limited to cases of penetrating brain injury of three to twelve days' duration. Almost all of them were infected with gram-positive pyogenic organisms, and about half were frankly suppurating. These wounds were excised, cleaned and closed, and injections of a solution of calcium penicillin were given every twelve hours for three days through a stab wound into the brain cavity. The average total dosage was 15,000 units. The penicillin-sulfanilamide powder was applied to the wounds during dressings and occasionally during operations, and a small number of patients with compound fractures in other parts of the body also received intramuscular doses of penicillin. The results in this group were encouraging. Gram-positive cocci usually disappeared from the wounds within forty-eight hours. The observers state that penicillin deserves an extensive trial in brain wounds for which definitive treatment cannot be given before seventy-two hours. For earlier cases they believe that the sulfonamides are adequately effective. Nonpenetrating wounds were successfully closed and treated with penicillin solution through tubes for three to five days, a total dose of only 3000 units being used. In scalp wounds not associated with fractures, healing by first intention was secured with a single application of 1 to 3 gm. of penicillin-sulfanilamide powder after excision.

Penicillin applications were also tried on a few burns that had remained persistently infected by hemolytic streptococci in spite of sulfathiazole by mouth and sulfadiazine locally. The response of these burns to extremely small doses of penicillin-sulfanilamide powder was uniformly rapid, and free grafts took satisfactorily in spite of the presence of pus containing gram-negative organisms. About 20,000 units was adequate in such cases.

No attempts were made by the British investigators to compare the results of penicillin therapy with those of other forms of treatment. Obviously this would have required extensive and carefully controlled studies and would have been futile unless it had been found that the penicillin itself was effective in the various conditions in which it was

used. They therefore confined themselves to ascertaining the range of usefulness of penicillin in the treatment of wounds, and the best methods of applying this form of therapy. The present results merely suggest that penicillin treatment is feasible and useful under certain field conditions. No claims are made that it is better than any other form of therapy. How useful it is and how it will compare with the results obtained with sulfonamides and other forms of therapy remain for further study.

The divergent results reported from the use of sulfonamides in the treatment of wounds illustrate well how difficult such a problem can be. Early reports of sulfonamide therapy were most enthusiastic, whereas in later ones the optimism was considerably tempered. This is illustrated in Meleney's recent report of the Subcommittee on Surgical Infections of the National Research Council.³ The members of this committee concluded from their extensive studies that sulfonamides minimize the general spread of infection in wounds and cut down the incidence of septicemia and death. They had no evidence, however, that the incidence of local infections was lessened by the sulfonamides as they have been employed. They state that, if the incidence of local infection in war wounds and burns is to be decreased, some other form of sulfonamide or some other bacteriostatic agent must be found that is effective against the contaminating organisms in the presence of damaged tissue. Penicillin is such an agent, and the studies of Florey and Cairns indicate that it may be useful by itself or as a supplement to the sulfonamides.

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MEDICAL EPONYM

STEVENS-JOHNSON SYNDROME

"A New Eruptive Fever Associated with Stomatitis and Ophthalmia" was described by Albert M. Stevens (b. 1884) and Frank C. Johnson (1894-1934) of Columbia University and Bellevue Hospital in the *American Journal of Diseases of Children* (24: 526-533, 1922). A portion of the article follows:

During a period of three months we had the opportunity of observing two cases of an extraordinary, generalized

eruption with continued fever, inflamed buccal mucosa and severe purulent conjunctivitis. . . .

. . . . No diagnosis could be made to correspond with the symptoms and course of the eruption in these two cases and no description was found of a skin condition in any degree comparable.

. . . . Here is a syndrome of dramatic onset, with fever, conjunctivitis and cutaneous eruption. The child is prostrated, the mouth and tongue are inflamed and raw, the eyelids are swollen and pus streams from the eyes. There is a course of three or more weeks of high fever, with leukopenia. The eruption, unlike any hitherto described, comes out progressively, for two weeks or more, matures and resolves in horny crusts, in the order of its appearance. The temperature falls with this resolution of the skin lesions. This syndrome suggests strongly an infectious disease of unknown etiology. We believe that this condition deserves to be considered a definite clinical entity.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CHASE — Lawrence M. Chase, M.D., of Carver, died February 8. He was in his sixty-first year.

Dr. Chase received his degree from Tufts College Medical School in 1904. He was a member of the Massachusetts Medical Society and the American Medical Association.

LANE — John W. Lane, M.D., of Dorchester, died December 3. He was in his sixty-seventh year.

Dr. Lane received his degree from Harvard Medical School in 1903. He was assistant demonstrator of anatomy at Tufts College Medical School from 1905 to 1908 and assistant in surgery, Courses for Graduates, Harvard Medical School, from 1912 to 1915. He served on the staffs of St. Margaret's, St. Elizabeth's and the Boston City hospitals. He was formerly a member of the Massachusetts Medical Society and the American Medical Association.

SULLIVAN — John T. Sullivan, Jr., M.D., of Boston, died December 10. He was in his seventy-first year.

Dr. Sullivan received his degree from Harvard Medical School in 1897. He was formerly school physician in Boston. He was a nose and throat specialist at the Carney and St. Elizabeth's hospitals and the Boston Sanatorium. He was a member of the Massachusetts Medical Society and the American Medical Association.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

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Fall River	March 27	Eugene A. McCarthy
Hyannis	March 28	Paul L. Norton

WAR ACTIVITIES

INDUSTRIAL HYGIENE

CARBON TETRACHLORIDE POISONING IN PARACHUTE FACTORY

The cause of illness among 135 employees in a Kentucky plant manufacturing parachutes was traced to carbon tetrachloride used for cleaning soiled spots on the chutes, according to an investigation by the Kentucky Division of Industrial Hygiene. The outbreak of illness occurred during a period of ten days and was manifested by abdominal cramping, nausea and vomiting. Some workers complained of "bloating and difficulty in breathing." Many employees were acutely ill and unable to continue work. The illness lasted from two to five days in the average case, although a number of workers continued to feel bad after resuming work.

The possibilities of food poisoning were ruled out by questioning of ill employees about food consumed in the forty-eight hours preceding onset of illness. The absence of fever and diarrhea indicated that the disease was not an intestinal disorder of bacillary origin. On further study, the nursing records revealed that a great many employees complained of frequent or even constant headaches, and complaints of gastric distress had been especially numerous for several weeks. The fact that the incidence of the disease was restricted to workers on the first shift, and to those whose work placed them in the same environment, pointed to some special factor such as a toxic chemical. A check of the records revealed that out of 137 sick employees, 135 had been engaged in sewing and cleaning the nylon used in manufacture.

It was found that more cleaning of the chutes had been done in recent weeks and that at times pure carbon tetrachloride had been used in place of the usual solvent. The solvent was kept in open containers, and an estimated 4 gallons were used daily. With the beginning of the cold weather season five or six weeks previously, ventilation was provided only by opening windows along the skylight, the side windows being closed. Since the fumes of carbon tetrachloride gas have a density 5.3 times that of air, they could only be removed by vents at the floor level. It was significant that the first noted symptoms were coincidental with the beginning of heating, and the consequent reduction of ventilation in an effort to conserve fuel.

The recommendation made for substitution of some other solvent was quickly adopted. The use of carbon tetrachloride was immediately ordered discontinued, and cleaning of parachutes is now being done with soap and water. — Reprinted from *Industrial Hygiene News Letter* (January, 1944).

MISCELLANY

HEMORRHAGE IN PULMONARY TUBERCULOSIS

In the life of any individual the sudden spitting of blood is a dramatic and fear-stirring event. Usually it is brought to the attention of the physician so promptly that an accurate and rapid diagnosis is possible. Self-neglect, however, is encountered on the part of some patients. Errors in diagnosis, too, are not unheard-of happenings. Thus there is every good reason why such an alarming symptom as hemoptysis must be viewed with concern by the doctor until the cause has been established and the proper emergency care and long-term treatment provided. In this regard, the following abstract of a recent article (Minor, G. R. Hemorrhage in pulmonary tuberculosis. *Am. Rev. Tuberc.* 48:109-114, 1943) is of interest.

Pulmonary hemorrhage is one of the most distressing phenomena encountered in medical practice. The patient is gravely alarmed and the physician is confronted by bleeding that comes from a point deep within a delicate organ enclosed in a rigid framework. To combat the bleeding there may be only slowly or doubtfully effective physiologic mechanisms.

Psychologic effects to one side, hemoptysis generally is indicative of serious pulmonary disease. It is recognized that unexplained blood-spitting must be considered due to tuberculosis until proved otherwise. Occasional causes, however, include such nontuberculous diseases as bronchiectasis, bronchogenic carcinoma, lung abscess, rheumatic

heart disease and various minor nose and throat affections. People apparently in good health and presenting negative physical signs and few or equivocal roentgenologic findings represent especially puzzling problems when they report having coughed up blood. In all cases it is essential that we exhaust every means at our disposal of tracking down the reason for obscure lung hemorrhage.

The causes of hemoptysis are still not clearly understood. Blame has been laid on deficiency in one of the factors concerned in blood coagulation, on tonic, nervous or endocrine factors, on erosion of a vessel wall by a tuberculous process, on rupture of a small aneurysm within a cavity. Although the most serious hemorrhages occur in old, fibro-ulcerative tuberculosis, small or moderate hemoptyses may be seen in early disease, sometimes as the first recognizable symptom. Softening of a lesion or progression of an established process may be accompanied by hemorrhage.

Among 1000 patients consecutively discharged from the Blue Ridge Sanatorium, Charlottesville, Virginia, only those were included in this study who gave a clear-cut history of spitting up 1 dram or more of blood, or who suffered a hemorrhage during their stay in the institution. "Streaking," "streaked sputum" and indefinite history of hemoptysis were excluded. In all, 905 cases of tuberculosis, made up of 424 males and 481 females, included 220 who had hemoptyses during the active phase of the disease. This is an incidence of 24.3 per cent, regardless of the duration of observation.

Some of the largest hemorrhages in this series occurred in a few patients showing bronchiectasis or rheumatic heart disease. Bogen, including instances of streaks and clots, found that over half his patients with hemoptysis expectorated less than 2 ounces of blood. The present study records 106 cases with hemorrhages of stated amount, ranging from 1 dram to 2 quarts, the average being 5 ounces. This did not include repeated bleeding from the same individual on the same or subsequent days, since these were not thought to be distinct episodes, but more or less a continuation of the first. In approximately 40 per cent of the cases the episode of hemoptysis was repeated at least once.

Hemorrhage was the presenting symptom, often the initial evidence of trouble, in 60 cases. Perhaps nothing drives a patient to seek medical advice faster than the expectoration of a single mouthful of blood, although 23 patients did not bring about their initial hemorrhage.

When the local physician was consulted by persons with hemorrhage in cases of previously undiagnosed tuberculosis 70 per cent were properly diagnosed, and it is estimated that 84 per cent correct diagnoses could have been reached by further study.

Only 49 cases in the entire hemoptysis group failed to show a cavity on x-ray examination, and of these, 11 were found to be nontuberculous. No less than 83.4 per cent of the tuberculous cases with hemorrhage had a positive sputum. Of the 170 patients in this latter category, 159 had roentgenograms revealing consolidation, honeycombing, punching out or frank cavitation.

Correlation of hemoptysis with physical exertion, with direct chest trauma or with mechanical disturbance of the lung is possible in some cases, although hemorrhage may and often does appear when the patient is at rest, perhaps during sleep. In only 28 cases in this study was there either a specific history of a precipitating factor or of its absence. In 10 patients hemorrhage was related to one or more menstrual periods.

Among the graver consequences of pulmonary hemorrhage must be listed strangling and asphyxia from massive bleeding, fatal blood loss in the cachectic patient, and the commoner and ever-present danger that blood from a cavity that is generating a positive sputum will spread the infection to other parts of the lungs, giving rise to an acute tuberculous bronchopneumonia or a massive caseous pneumonia. Obviously, repeated episodes of blood-spitting multiply the chances for such complications to occur.

Summary and Conclusions

In a study of 1000 sanatorium tuberculous patients it was found that hemorrhages occurred in 24.3 per cent of them.

The average size of hemorrhage was 5 ounces. Forty per cent of hemorrhages were eventually repeated.

In 60 patients, the first remarkable symptom was hemoptysis.

Seventy per cent of cases with a history of hemorrhage before diagnosis were properly diagnosed by the local physician, when he was consulted. Thirteen per cent, however, were misdiagnosed.

Most tuberculous patients with hemorrhage have cavitation visible on x-ray examination; 83.4 per cent of this series had a positive sputum.

Trauma to the chest, strenuous exercise, mechanical disturbance of the lungs and, in females, the menstrual period are definite precipitating factors.

Small hemorrhages often occur from early lesions at the height of the catarrhal and toxic symptoms that probably signify softening. These are not usually serious and may, in the long run, be beneficial if they call attention to an undiagnosed tuberculosis. The larger hemorrhages that occur in chronic ulcerative tuberculosis, however, although rarely immediately fatal, are accompanied by many unpleasant and dangerous possibilities. Of the 12 deaths that occurred in the sanatorium after hemoptysis, it is thought that 5 were directly or indirectly the result of the hemorrhage. — Reprinted, in part, from *Tuberculosis Abstracts* (January, 1944).

NOTE

Dr. Bennett F. Avery, dean of Boston University School of Medicine for the past three years, has recently been appointed director-general of public health of Iran. Since Dr. Avery was formerly a resident of the Near East, he is well fitted to assume this new responsibility. Although the date of his departure from the United States is indefinite, he has already severed his connections with the medical school.

CORRESPONDENCE

DYSENTERY

To the Editor: I was quite interested in the editorial "Dysentery" in the January 6 issue of the *Journal*.

Under the conditions the diarrheal diseases render their separation impossible. The dysenteries in the military service are specifically diagnosed, and I doubt if the rate is any better in civil life. As expressed in a recent paper [*Dysenteries and diarrheas. War Med. 4: 459-464, 1943*], I do believe, however, that a practical differentiation of noninflammatory diarrhea from inflammations of the intestine can be made by a simple examination of the stool for exudate, and in many cases this examination will indicate the proper treatment before a therapeutic test is instituted.

I should also like to suggest that the use of emetine makes a much more satisfactory therapeutic test for amebic infection with symptoms than does that of either carbarsone or yatren, both of which require a considerable number of days before the therapeutic effect is evident.

COLONEL GEO. R. CALLENDER, M.C., U.S.A.

Army Medical Center
Washington, D. C.

NEED FOR MEDICAL AND SURGICAL SUPPLIES

To the Editor: There is a critical need for medical and surgical supplies that may lie hidden and forgotten in physicians' offices; discarded or tarnished instruments, surplus drugs, surplus infant foods and so forth. Collected, packaged and used, they can be of great help to the armed forces.

Surgical instruments and medicines are hungrily snatched by the medical corps of our allies. The work of war-zone hospitals and welfare agencies is too often crippled by the lack of medical supplies. Community nurseries in this country, and refugee camps abroad cry out for vitamins and baby foods for their ill-nourished charges.

The committee's roll call of medical requests — not one of which has been turned away — reads like a world geography: the Fighting French in North Africa and Tahiti; the Royal Norwegians in Canada and Iceland; the West Indies; South and Central Africa; China; India; Great Britain;

Yugoslavia; Greece; Syria; Russia; Alaska; and, of course, the United States.

To meet the demands that pour into headquarters, the committee needs all types of instruments, especially clamps, scalpels, forceps and all kinds of drugs, from iodine to sulfonamides. By contributing what they can spare, physicians will help speed another shipment of sorely needed medical aid.

JOSEPH PETER HOGUET, M.D., *Medical Director*
Medical and Surgical Relief Committee

420 Lexington Avenue
New York City

FLUORINE AND DENTAL HEALTH

To the Editor: In recent numbers of the *Journal* there have appeared a report of a committee of the Massachusetts Central Health Council, entitled "The Dental Needs of Massachusetts Children of Today," and also two editorials, one referring to this report and the other dealing with a council report, "Problems of Local Health Officers." It is a great satisfaction to find the *Journal* so willing to publish this important report, and to lend editorial comment to the fundamental work that the council is doing.

I doubt if all your readers know exactly what the Massachusetts Central Health Council is, even though the Massachusetts Medical Society is a member. It is composed of about a score of organizations, both official and nonofficial, that are carrying on work relating to public health on a statewide basis. These include the Massachusetts Department of Public Health, the Massachusetts Department of Labor and Industry, the Massachusetts Medical Society, the Massachusetts Public Health Association and similar agencies. It also includes as constituent agencies, city or town councils that themselves represent on the local level the same kind of "organization of organizations" formed for the purposes of co-operation, deliberation and collective action. Such organizations represent democracy at work in public health.

I want, especially, to make a brief comment on the report of the Dental Committee and the editorial thereon. As one concerned primarily with public health I have been greatly interested in the possibilities of the application of the recent work on fluorine and its relation to dental health as a community project. Here for the first time we seem to have a genuine prophylactic for dental caries that can be promoted as a public-health measure. The report itself devotes a short paragraph to this most important possibility, and the editorial does not even refer to it.

As in the case of cowpox virus, nature seems to have anticipated science, and the preventive phenomenon has been operating in certain communities for generations before being interpreted by McKay, Dean and others. It now seems well established that in amounts of one part per million and over, fluorine in drinking water reduces the prevalence of dental caries. In amounts appreciably above this it causes discoloration or dental fluorosis (so-called "mottled enamel"), with its accompanying disfiguring effects, but still showing a strikingly lowered incidence of caries. By analysis of the teeth of persons and of experimental animals it has been shown that fluorine in water or other articles of diet is metabolized, or in some manner incorporated into the tooth structure, presumably making the enamel more resistant to acid corrosion due to fermentation by *L. acidophilus*.

It also seems to be well established that the topical treatment of the teeth with fluorine compounds has a similar inhibitory action against caries. Therefore, private dentists and dental health clinics have at their disposal a true prophylactic that may be used for the benefit of the patient.

There remains the problem of whether fluorine in prophylactic amounts has any undetected deleterious effects of a cumulative nature, as well as the question of the control of dosage. Since a large number of people have for many years been exposed to public water supplies containing fluorine greatly in excess of the proposed prophylactic concentration, it should be possible to analyze the vital statistics of these populations and to examine the present physical state of health of these people in order to find the answer to the first question reasonably soon. The question of dosage in water seems relatively simple, since equipment similar to that now used for chlorine will serve. Even adjustment of dosage to

meet the requirements of the relative water consumption at different times of year could be provided.

Fluorine in finely ground bone meal as a universal constituent of the diet has similar possibilities.

The topical treatment of the teeth with fluorine is strictly a dental practitioner's problem, which will surely be explored by that profession.

Of course, caution is indicated in any procedure that affects the general public health, and we must be as sure as we can be that a prophylactic measure will not boomerang. Nevertheless, there must be some venture in every new public-health or medical practice, and we must weigh the gains against the possible risks. Perhaps we have been more guilty of caution than daring in some cases — witness the lag in accepting pasteurization, for example.

I am confident that we have at last a weapon for the practice of public-health dentistry. We shall, in a few years, provide for the incorporation of fluorine in some universal article of diet, and local application of this chemical will become common. Let us be ready and not block this great beneficent discovery of a means of attacking man's most ubiquitous disease by any false prejudice or supercaution.

CURTIS MORRISON HILLIARD

Simmons College
Boston

RESULTS OF BOARD EXAMINATION IN NOVEMBER, 1943

To the Editor: Attached is a tabulation of the results of the examination given by the Board of Registration in Medicine on November 19, 1943, listed according to the medical school from which the applicants graduated.

H. QUIMBY GALLUPE, *Secretary*
Board of Registration in Medicine

State House
Boston

MEDICAL SCHOOL	No. PASSED	No. FAILED
Boston University School of Medicine	3	0
College of Physicians and Surgeons, Boston ..	0	18
Harvard Medical School	2	0
Massachusetts College of Osteopathy	0	9
Middlesex University	60	83
Tufts College Medical School	6	0
Chicago Medical School	7	2
Columbia University College of Physicians and Surgeons	2	0
Georgetown University	1	1
Jefferson Medical College	1	0
Johns Hopkins University School of Medicine ..	1	0
Kansas City University of Physicians and Surgeons	5	41
Kirkville College of Osteopathy and Surgery ..	0	3
Mid-West Medical College	0	6
Missouri College of Medicine and Science	0	1
Northwestern University	3	0
Ohio State University	2	0
Philadelphia College of Osteopathy	1	3
University of California	1	0
University of Maryland	1	0
University of Minnesota	2	0
University of Rochester	2	0
University of Berlin	0	1
University of Bologna	1	3
University of Breslau	0	1
University of Geneva	0	1
University of Hamburg	0	1
University of Heidelberg	1	1
University of Jena	0	0
University of Karl Franzens	1	1
University of Karlova	0	1
University of Kazan	0	1
University of Königsberg	0	0
University of Köln	1	2
University of Lausanne	0	1
University of Laval	0	1
University of Leipzig	0	0
University of Marseilles	1	0
University of Paris	2	1
University of Pisa	0	2
University of Prague	0	1
University of Regia	0	1
University of Tartu	0	1
University of Vienna	0	1
Totals	106	189

(Notices on page xv)

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PROPOSED EXTENSION OF THE SOCIAL SECURITY PROGRAM, WITH SPECIAL REFERENCE TO HEALTH AND MEDICAL ASPECTS*

I. S. FALK, Ph.D.†

WASHINGTON, D. C.

HISTORICALLY, it is peculiarly fitting that this conference should consider the health aspects of social-security plans. It was here in Massachusetts that the public-health movement of the United States received much of its first great impetus. And it is especially significant that in the classic *Report of the Massachusetts Sanitary Commission* (1850), Lemuel Shattuck saw and showed clearly not only the interrelations among poverty, sickness and dependency but also the potential role of health services in the welfare of society and the pursuit of happiness.

In the ninety-three years that have elapsed since the appearance of the Shattuck report, there have been advances in environmental sanitation and other aspects of public health that have transformed society. Medicine has become a science and has attained high levels of effectiveness. But it remains to organize the health services so as to assure the availability of modern medical services to all who need them and can benefit from them. The proper test is not that health is better today than it was a decade or a generation or a century ago or than in some other country, nor that medicine and public health accomplish more now than they did then. By such comparisons, health provisions were good in 1900 and perhaps even in 1850. The valid test is whether we do well and effectively today what we know how to do and can do. By this test there is no ground for complacency.

For this audience it is unnecessary to review the fundamental importance of health measures and of medical care in the prevention of destitution and in the building of a strong and democratic society. You see in your own work the extent to which sickness, disability and postponable death destroy the economic independence of persons and families. You know that much suffering and dependency could have been prevented by adequate and timely service. You are aware of the opportunities for therapy or rehabilitation that are missed because there is no

way of paying for needed services. Those of you who have been especially concerned with the problems of children know to what extent society is failing to utilize modern medicine to protect and strengthen the generation that will soon inherit this country.

The public was shocked by the number of young men — about half of the first 3,000,000 called up to serve in the armed forces — who were rejected because of diseases and physical defects, many of which could have been prevented or were still remediable. There is a widespread and insistent public demand that these and similar conditions shall not continue: that this country shall come into the heritage of health services and health security made possible by the progress of science and the wealth of the Nation's resources. This demand has not come primarily because of new or startling discoveries in the laboratory or clinic. It has emerged, by almost imperceptible degrees, from public education — from knowledge of what modern medicine can do through effective and general application, and from awareness that there are ways of accomplishing such application. It is therefore not surprising that the demand for strengthened and broadened health services takes practical form within the framework of plans for social security.

The fullest measure of security rests on the assurance of opportunity to work and earn a living in an economy organized to produce abundantly. To whatever extent this goal is met, social security must also include provision for continuity of income during periods when family livelihood is threatened by sickness or by the unemployment or premature death of the breadwinner, or by his disablement or retirement in old age. World-wide experience has shown that social security in this narrower sense of income maintenance can be most effectively attained through comprehensive contributory social-insurance measures supplemented by public assistance to meet individual needs. New plans for social security will not be complete or economically sound unless they include measures designed to make avail-

*Delivered at the Massachusetts Conference of Social Work, Boston, December 2, 1943.

†Director, Bureau of Research and Statistics, Social Security Board

able to every member of the community certain basic services — among the most important of which are the health services.

* * *

The objective of an adequate health program for these times can be simply stated. There must be assured for all persons access to all essential services, including both preventive and therapeutic services, according to the medical need and without regard to their ability to pay at the time the services are received.

With some important exceptions to be mentioned later, this country has in peacetime a nearly adequate volume of medical facilities and a nearly adequate number of physicians. Unfortunately, neither the facilities nor the medical personnel is distributed throughout the country entirely in relation to the need for services. Moreover, the existing resources of facilities and personnel are not in fact available to large numbers of persons who cannot surmount the barrier of costs that stands between them and the doctor, the laboratory or the hospital. Large numbers of persons go without badly needed care, hesitant to undertake financial burdens or, where these are available, reluctant to accept charity or free services. The practice of modern medicine, moreover, calls for the use of a variety of necessarily costly laboratory technics and specialized skills and equipments that are not available in the office of the ordinary physician. With every passing year, medicine becomes a more intricate and more complicated science, demanding the co-ordinated skills of general practitioners, specialists, laboratory technicians and the hospital. The modern medical schools train young men and women to practice co-ordinated medicine, as members of groups and teams. Yet — outside hospitals — medicine continues to be practiced primarily by more or less isolated persons. Although organized practice develops, its growth is at less than a snail's pace. Each advance in medical science underscores the need to solve problems relating to the costs of medical care and the need to co-ordinate services.

The financial solution — access to needed services without barriers of cost — may be attained through either of two major patterns. Both community health services and personal medical care may, like education, be provided as a public service. According to this pattern, governmental agencies would finance the program from general tax revenues, and would provide all needed facilities and hire all needed personnel. Every member of the community would be entitled to call on these services to whatever extent he needed them. This would be "public medicine" or "state medicine" — using these as descriptive terms rather than as emotional epithets. There is a great deal of "public medicine" now, and its volume grows steadily.

On the other hand, the community health services alone — sanitation, control of communicable diseases and other public-health measures — might continue as government services, supported from general taxation, whereas medical services for the individual would be provided through a contributory social-insurance system. In this case, medical care would be financed through regular contributions to a social-insurance trust fund made by all employed workers — whether self-employed or employed by others. These contributions would entitle insured workers and their dependents to receive all needed services without further payment; the doctors, laboratories, hospitals and other groups would be paid for their services by the social-insurance fund. Contributions might also be made on behalf of other groups in the population, — social-insurance beneficiaries, recipients of public assistance, persons engaged on public works projects and persons in the armed forces, — who would thus become member of the social-insurance system and entitled to medical care on the same basis as workers who have contributed from their earnings. Thus, virtually the entire population would receive medical service through the social-insurance system.

It will be readily appreciated that the first of the two major alternatives — public medical service — would involve the more extensive changes in present medical practice. Many persons argue that because it offers the greater — perhaps the only — assurance that medical care will be available to everybody who needs it, public medical care is the alternative to be preferred. In countries where modern medical facilities and trained personnel are limited, government provision of hospitals and clinics and operation of these facilities with salaried medical personnel may offer the greatest promise of speed and effective health protection. For the United States, however, it might not be considered so practicable or, at any rate, so acceptable a pattern.

At all events, directing my attention primarily to social-insurance possibilities, I shall not explore farther the possibilities of a general public medical service. I shall discuss at this time only the question whether all the major objectives can be achieved through co-ordinating community health services provided by general tax funds and individual medical care financed through social insurance. A properly designed social-insurance system, built on existing medical practices and arrangements, could assure access to needed medical services for 90 per cent or more of the population at the outset, and eventually for every group that should obtain the services through the system. Such a plan would have a solid financial foundation.

The medical services of a comprehensive social insurance system should, of course, be co-ordinated with cash benefits, which assure continuity of income when earnings are interrupted by temporary or permanent disability, thus providing the means

subsistence without which medical care may be meaningless.

* * *

If the objectives discussed earlier are to be achieved, the social-insurance system must cover all workers. Building on the present old-age and survivors' insurance system, it might be said that in addition to the employments now covered, it should include agricultural labor, domestic service, government employment, employment for nonprofit institutions, self-employment in both agriculture and business and miscellaneous employments now excluded. With such a coverage, the insured workers and their dependent wives and children would normally constitute about 85 per cent of the population. As suggested earlier, other persons — such as the needy and the social-insurance beneficiaries — might be qualified to receive medical care through contributions to the social-insurance system made on their behalf.

Under a unified social-insurance system of which medical-care insurance was a part, there would need to be only a single contribution to the insurance fund for all types of benefits. Employers would submit one pay-roll report, and self-employed persons a single report of income. The same earnings records would serve for determining rights to any type of benefit. The funds available for particular types, however, might be segregated. It would probably be necessary to set aside a definite proportion of the contribution income to pay for medical services.

Ideally, the social-insurance system should include provision for any needed medical service — services of the general practitioner and the specialist, use of laboratory and x-ray facilities, hospitalization, dental care, home nursing and prescribed drugs, medicines and appliances. At the outset, however, it might be necessary to provide more limited benefits — not because people are unwilling to pay for all types of services, but because facilities and trained personnel are lacking to furnish some of the services to all persons who need them and who would seek them if the present barriers of cost were removed. This is the situation particularly with respect to dental care. Home nursing presents similar problems, in addition to the need for extensive adjustments in the arrangements under which the service would be furnished. Consequently, it would be wiser to omit these services at the outset, but to provide for their inclusion as soon as practicable. It may also be undesirable for the social-insurance system to meet the costs of any except unusually expensive medicines and appliances.

With these limitations, the insured worker and his family would still have access to a group of medical services that lend themselves to sound integration: care from the family physician, together with specialist services, laboratory and other diagnostic and therapeutic facilities, hospitalization and

unusually expensive prescribed medicines and appliances. This limited program provides a suitable base from which to build toward the more comprehensive provisions. Initially, an amount equal to 3 per cent of pay rolls would probably suffice to furnish insured persons with the guaranteed services and commodities, and to provide adequate remuneration to doctors, hospitals, laboratories and others.

In a nationwide, comprehensive system of social insurance there must be central determination of policies and standards to assure equitable treatment of all members of the system. But the actual administration of the social-insurance benefits should be highly decentralized. Benefits would be claimed at or through local social-insurance offices, and all determinations requiring knowledge of local conditions or personal circumstances should be made in the local communities.

In the case of medical-care benefit, it is particularly important to distinguish between the functions of centralized policy making and decentralized operation. In the first place, the social-insurance system would build on existing facilities, personnel and arrangements, utilizing existing practitioners, hospitals, laboratories and other personnel and facilities. It need not and should not interfere in any way with the essential professional aspects of medical practice or with the internal management of hospitals.

If medical-care benefits were to become available, most persons who had a family physician would presumably continue to go to him. Others would select a physician from among all those available in the community. The only essential change that the insurance arrangement makes between physician and patient is in the method of payment. Instead of paying for medical service at the time it is received — when perhaps he can least afford it — or incurring a heavy debt, or unwillingly accepting free care or going without needed care because he cannot pay, the insured worker would pay for medical care for himself and his family by small deductions from his earnings when he is employed. Instead of each family's carrying the cost of its own care, whether that cost were extremely light or unbearably severe, every worker would pay only his proportionate share of the average cost. Every employed person can afford to contribute an average percentage of his earnings; it is the unequal incidence of medical costs that makes them a burden to the individual and a threat to family security.

Just as each worker could choose his physician from among all licensed practitioners of medicine who wished to participate in the insurance arrangement, so every physician would have the right to accept or reject patients. Social insurance would enable the physician to engage more fully in the practice of medicine, utilizing all modern techniques and laboratory aids, and calling on specialists for

advice or service when needed, without concern for the patient's inability to pay. The physician would also know that he would be paid for all his services to insured persons.

The arrangements to pay physicians might take several forms, among which those in each locality would choose whichever they preferred. Physicians might be paid according to established fee schedules for each home visit, office visit and so on. Fee schedules could be uniform for the entire country or might vary from one region or place to another, taking account of variations among communities in customary fees and in overhead costs of practice.

The method of payment that has come to be preferred by physicians in Great Britain, after considerable experience with fee schedules, is known as the capitation method. Under this method the physician receives a fixed amount per year for each person who chooses him, whether he is called on to give much or little or no service to any particular patient during the year. This method requires that every insured person specify his intention to be on some physician's list. So that physicians will not lose income to which they are entitled, capitation payments are made not only for those who have chosen a physician but also for those who have not. Such payments and adjustment are, of course, made locally and not from the central office.

Physicians who so choose might be paid on a salary basis, whole time or part time; or a combination of various methods might be used. Provisions should also be made for equitable payments to organized groups of physicians.

The hospitals, like the physicians, should be free to choose the method by which they would be paid. In discussions that we have had with hospital administrators and official committees of the hospital associations, it has been generally agreed that payment should be made direct to the hospital, whether by assignment of a fixed benefit amount for each day of hospitalization or by payment of the reasonable cost of minimum necessary services, within fixed minimum and maximum limits. The method of payment to hospitals should not and need not interfere in any way with the hospital's control of its own customary management and affairs.

With such a general framework for medical services furnished through social insurance, the current pattern of professional relations among people, doctors and hospitals would not be changed in any basic way. This is the virtue of health insurance to those who wish to build by slow and measured evolutionary processes on the status quo.

* * *

If the approach to a health-insurance plan is primarily with respect to existing financial problems, the tendency is to leave treatment of the qualitative problems largely to the operation of *forces and trends* working within the professions. This is not to say,

however, that an insurance plan designed along these lines should be or can be indifferent to the need for safeguarding and constantly improving the quality of services provided as insurance benefits. On the contrary, when contributions are compulsory, government cannot avoid responsibility for the quality of the benefits.

In a system that builds on the existing and available resources in professional personnel, hospital and other facilities, I suggest that at least the following six provisions are essential to protect and promote the quality of the medical services: access to necessary specialist and consultant services; specific rates of payment for services of the specialist when furnished by physicians who meet professional standards certifying their special skill; access to necessary laboratory and related aids to diagnosis and treatment; payments for hospital care furnished in institutions that meet medical and hospital professional standards applicable to institutions offering general or limited varieties of service; specifications that aid the development of organized group practice and co-ordinated medical, hospital and community health services; and financial support for professional education and for research.

In establishing professional standards, the insurance system should obviously be expected to lean heavily on standards developed by professional organizations. A competent advisory council, with adequate professional representation, would be essential.

The professional specialty boards have already done basic spadework in certifying most of the qualified specialists in medicine. Large problems remain, but desirable solutions can undoubtedly be found by administrators working in close collaboration with advisory bodies.

In designating hospitals entitled to receive payments, the social-insurance system may be guided by existing accrediting procedures long accepted by the Nation's hospitals. Institutions that cannot meet all the standards applicable to large urban or metropolitan hospitals might nevertheless be accredited for all or limited varieties of cases, if the service were adequate to promote the health and safety of the hospitalized persons. The social insurance system might also encourage the development and use of qualified institutions for the care of the chronic sick or of corresponding facilities associated with general hospitals, thus providing more appropriate treatment for chronic patients and reserving the more elaborate and more expensive facilities of the general hospital for acute cases.

General policies for the acceptance of participating hospitals, the designation of specialists and the arrangement for paying doctors and hospitals should be determined centrally for the social-insurance system. These are functions of the administrative body, guided or directed by consultations with appropriate professional and other advisory bodies. Appropriate

Education of those policies, however, should be carried out through a thoroughly decentralized administration, operating at every level of administration, from the central to the local, with the help of advisory bodies that include representatives of the persons who furnish and those who pay for the benefits.

I have stressed the point that a social-insurance system would be built on existing facilities and existing arrangements for medical care, changing primarily the methods of payment. I do not wish, however, to give the impression that the health services would remain in their present stage of development. By striving to give every physician access to all necessary diagnostic and therapeutic aids in the treatment of every patient, whatever that patient's economic circumstances, the system would advance the practice of medicine toward the standards that now prevail in the better hospitals and clinics. By removing the barriers of cost that today cause many persons to postpone seeking medical advice, it would stimulate early diagnosis and treatment and thus aid in the prevention of much illness and disability. By guaranteeing physicians fair payments for their services, it would enable them to practice in areas and communities that at present cannot provide them with a decent living. By guaranteeing payment for hospital service, it would encourage the building of hospitals and health centers in communities that can find the capital funds for such construction if they are assured of a continuing operating income.

There is an additional obligation to take certain direct measures to improve the adequacy of existing health and medical services. Either from the social-insurance funds or from other public funds, money should be made available to construct hospitals and health centers in communities that cannot raise the necessary capital. Moreover, as indicated before, to advance the skill and knowledge that will promote prevention of disease, and to assure progressive improvement in the quality of medical care, the social-insurance system might properly set aside a small fraction of the income from contributions for the support of research and of professional education and training.

* * *

Among physicians who accept the need for medical-care insurance, some will criticize the plan outlined here as far too conservative and too timid. In particular, this group will object especially to permitting fee for service as one method of payment.

There is little doubt that some of the most serious deficiencies of present-day medical practice result from the fee-for-service method of payment, because it discourages early, preventive or adequate care — especially among people of modest means — at the same time that it puts a premium on excessive treatment in some cases and inadequate treatment in others, and on various types of fee-splitting prac-

tices. Some of these objectionable features would be carried over into the insurance system, despite precautions that might be taken. Although the patient would no longer be barred from needed services, there would be a risk that some physicians would load unwarranted service charges on the insurance fund. Since the aggregate amounts available for all payments to physicians would be limited, the result might be a competition for patients and for volume of services almost as inimical to professional standards as that which occurs today. Through the downward proration of physicians' bills if they are excessive, the insurance fund can be protected against extreme unwarranted costs. For the rest, the problem would be largely a matter of intra-professional controls.

Practitioners here, like those in Great Britain, would probably turn to a capitation or a salary basis of payment, because they would learn by experience that these methods are more satisfactory for them as well as for their patients. Nevertheless, I do not agree that the insurance system should bar the fee-for-service method. So long as a majority of physicians prefer or insist on a fee basis, it should be accepted by the social-insurance system. At the same time, it should give full opportunity for the development of organized group practice where this arrangement is preferred by physicians and insured persons. In other words, the insurance system should build on what now exists, and at the same time should build toward better arrangements by leaving latitude for change and improvement as rapidly as change is desired by or is acceptable to those who are most concerned.

Certain misleading criticisms of medical-care insurance that are being broadcast across the Nation can be dismissed in a few words.

In the first place, medical benefits furnished through social insurance are not "free medicine" or "free care." It is of the essence that social insurance is contributory, and that people pay for what they get.

In the second place, expenditures for medical care through social insurance need be no greater than the amounts the population already spends in a hit-or-miss fashion. In supporting a larger volume of service and better service, more would be spent for the types of service included as insurance benefit than is customarily spent. Such an increase would be offset by savings from curtailing present levels of expenditures for useless services and services now furnished uneconomically. Moreover, paid in regular, budgeted and average amounts, the insurance costs would not be burdensome or catastrophic for anyone, even if in the aggregate they were somewhat larger than the total amount now spent individually for medical care. They would be absorbed in an orderly fashion into the streams of the social economy, just as the contribution costs of workmen's compensation, old-age and survivors in-

insurance and unemployment compensation have been absorbed.

Thirdly, the medical-insurance system would not destroy the private practice of medicine. It would strengthen and preserve its really essential elements — competition for patients or for annual income on the basis of satisfactory service, not on the size of a fee; free choice of his physician by the patient and the right to change to another; the right of the physician to accept or reject patients; the right — and also the obligation — of the profession to participate in the determination of all matters of high policy that affect medical practice; and the opportunity of the practitioner to be wholly concerned with his patient's medical needs irrespective of the latter's pocketbook.

Fourthly, the medical-insurance system would not weaken or destroy the voluntary-hospital system. On the contrary, it would preserve to these hospitals their control over their own institutions and would guarantee them increased and assured continuity of income so that their services to the public could be larger and better.

Last of all, the medical-insurance system need not and should not ignore noninsured needy persons. As pointed out earlier, through payments made on their behalf by public agencies, the needy could be made entitled to the services provided for self-supporting families. Thus, one class of service would be available for all, with dignity and self-respect for the patients, whereas physicians would be released from the concern to distinguish pay from part-pay and free patients. This arrangement would be more satisfactory than present or prospective programs of medical assistance, even with the improved financial arrangements under the Social Security Act already recommended by the Social Security Board.

* * *

With what assurances or what hopes can one look forward to more adequate health protection than the people of the United States now have?

The formulation of objectives and methods is only the beginning. A specific program of action was recently proposed to Congress through a bill (S. 1161) introduced in the Senate by Senators Wagner and Murray and in the House (H.R. 2861) by Representative Dingell. This bill is notable in that for the first time it sets forth a comprehensive national program of contributory social insurance, including provisions for medical care in sufficient detail to provide a basis for public discussion. Submitted by its sponsors not as a final blueprint but as a basis for public discussion, its proposals deserve and invite thorough consideration, reasoned debate and constructive criticism.

I believe that the great majority of the people of this country know that the objectives of medical-care

insurance are sound; they want more nearly adequate service and are prepared to pay for it. The public and all the agencies of the Government most directly concerned — legislative and executive — need the help of persons with a professional background and knowledge to bring to light what is unsound in any specific plan that is proposed, and to discover what sound and constructive changes are desirable.

There is not much time for public education and discussion if the opportunity of achieving a comprehensive and well-designed system of social security in our time is to be grasped. If action is postponed until the potential disruptions and crises of the postwar period are upon us, we may find ourselves with a hastily devised and inadequate relief program, rather than a soundly conceived social-insurance system. Once the general principles of a social-insurance program have been agreed on, time is needed to work out detailed plans and procedures and administrative machinery. It would probably be possible to move fairly rapidly in extending the cash-benefit system, for which a substantial framework already exists. No responsible administrator would, however, want to begin operation of a medical-care-insurance plan until he had had adequate time for consultation with all the professional and lay groups whose interests and knowledge and skills should be utilized in developing detailed policies and procedures.

A period of full employment like the present is the most favorable time for initiating a contributory social-insurance program. The initial impact of the contributions can be more easily borne by workers and employers than at any other time. The new contributions will have a deflationary effect on the social economy whenever a beginning is made. Deflationary pressures are needed now; they might not be wise in the immediate postwar period.

If social-insurance coverage is extended to all types of employment during the war, the great majority of the workers will come to its end with right to cash benefits for themselves or their dependents in case of unemployment, sickness, disability, retirement or death, and with access to medical care for themselves and members of their families. If extension of the system is postponed until a period of limited employment, it may be years before large groups of workers can qualify for insurance protection.

If it is decided now that medical-care insurance is wanted, and if the detailed plans are developed now the tens of thousands of physicians and surgeons who are serving in the armed forces will, on their return find opportunities for civilian service, with more latitude for choice as to how and where they will serve than they have had before. If each returning physician must make his way back into practice wherever his chances seem best for establishing an adequate livelihood, it may take a long time to bring

about a relocation of physicians and medical facilities in accordance with the needs of the population.

Now — before the war ends — is the time to plan the peace for the years ahead. Such planning must be world-wide. But it must also be national and local. And it must comprehend not only political security but economic and social security — freedom from

want and from the fear of want — in order that men may live lives of dignity and human worth. Social security thus appears as a necessary condition for men to be free and independent.

There is increasing recognition that health protection would be among the most valuable, the most potent for the future, of all the benefits from a comprehensive program of social security.

THE BLUE CROSS, THE BLUE SHIELD AND THE WAGNER-MURRAY-DINGELL BILL*

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BOSTON

PREPAYMENT insurance for protection against the cost of sickness is generally accepted as sound. The hospital plans of the Blue Cross, started a little over ten years ago, now operate in thirty-six states and the District of Columbia, which contain 87 per cent of the population, with over 13,000,000 subscribers. The medical plans of the Blue Shield started later, are now operating in thirteen states, which contain 50 per cent of the population. Both organizations are growing rapidly, with subscribers from both urban and rural areas. Both are on a voluntary basis and are nonprofit organizations operating under the direction of state insurance commissioners but controlled by directors, a majority of whom are representatives of hospitals in the case of the Blue Cross, and physicians in the case of the Blue Shield. Thus, both are directed by those most interested in the success and progress of these bodies.

There is not much use in proclaiming the virtues of something that is already accepted as admirable. Almost everybody agrees that the Blue Cross and the Blue Shield are good. But are they good enough? Many persons believe that they are sufficient to meet the need of a method of protection against hospital and medical costs and that they will gradually expand geographically to cover all parts of the United States and will add benefits to cover all medical needs. Admittedly, this will be a gradual evolutionary process, elastic enough to fit every area and every changing need.

Others say that voluntary plans, dependent on personal volition, will never adequately protect the community against sickness. They hold that such plans are too slow in operation, pointing out that in ten years only 13,000,000 out of a possible 80,000,000 persons have availed themselves of the Blue Cross; that many who need protection will never avail themselves of it; that the Blue Shield is too limited in benefits to give satisfactory protection; and that it will be necessary either to supplement voluntary plans with compulsory plans or, better still, to replace

these imperfect voluntary plans by a comprehensive, compulsory plan embodying medical care in the home, office and hospital, together with such hospital care as is needed.

We are now called on to face this problem of the comparative merits of voluntary and compulsory health insurance through the submission to Congress of the Wagner-Murray-Dingell Bill, which proposes such a system of compulsory health insurance as part of a unified national insurance system for the entire United States.

What is the Wagner-Murray-Dingell Bill? To estimate its value intelligently, which incidentally will help one to decide on the merits of voluntary and compulsory insurance, one must at least understand its essential provisions. For the purpose of this discussion the following are the most important factors. The introduction to the bill reads as follows:

To provide for the general welfare; to alleviate the economic hazards of old age, premature death, disability, sickness, unemployment and dependency; to amend and

and extend the social security rights of individuals in the military service [they are not protected now]; to provide insurance benefits for workers permanently disabled; to establish a federal system of unemployment compensation, temporary disability, and maternity benefits [now under state control]; to establish a national system of public health service; to establish a federal system of medical research; to advance the advancement of knowledge and skill in the provision of health services and in the prevention of sickness, disability and premature death [this is extension of public-health services and financial assistance to medical schools and medical research]; to enable the several states to make more adequate provision for the needy aged, the blind, dependent children, and other needy persons; to enable states to establish and maintain a comprehensive public assistance program; to amend the Internal Revenue Code.

Concerning the intent of this bill to improve living conditions in the United States and to make this a happier land, there can be no doubt and no opposition. The question is whether the method will accomplish the results desired. To determine this the general principles underlying the operation of the provisions of the bill must be reviewed and its specific measures examined. The primary concern here is with the medical and hospital section.

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Perhaps the most important item in the bill is that of federalization. Can the federal government do this better than state governments? In some ways it can; for instance, such federalization assures similar application in benefits in all states, whereas at present there is variation in the action of security boards in different states. On the other hand, can a centralized organization ever understand and adjust its rulings and methods to meet satisfactorily the varying local conditions of forty-eight states? Will the resulting bureaucracy that must of necessity be created by such federalization further accentuate the already alarming number of federal employees, with the corresponding dangers of political patronage and the party coercion of voting powers?

Certainly this bill presents a fascinating blueprint of governmental paternalism, professing a most kindly interest in the economic welfare of its citizens and setting up an attractive medical and hospital structure to provide for care in sickness and to develop preventive measures. Again, there can be no quarrel with the desirability of the goal or the intent; the only question is whether the result can best be obtained in this way. It is a pretty picture, but is it a true one?

What are the essential points of the medical and hospital section? Title IX provides:

Every individual who is currently insured and has been found by the Board to be eligible for benefits under this title in a current benefit year, shall be entitled to receive general medical [that is, medical care in home, office or hospital], special medical [that is, care by surgical and medical specialists in home, office or hospital], laboratory and hospitalization benefits.

Moreover, all dependents of the insured receive the same benefits.

The administration of all this is placed under the Surgeon General of the Public Health Service, who is authorized to negotiate agreements with appropriate agencies of the United States, or of any state or public or private agencies, or with private persons, to utilize their services and to pay fair, reasonable and equitable compensation for them; that is, he may select physicians, specialists and hospitals. The National Advisory Medical and Hospital Council is set up with the Surgeon General as chairman and with sixteen members appointed by him from a panel of names submitted by professional and other agencies and organizations connected with medical services and education and with the operation of hospitals, and from other organizations informed on the need for or the provision of medical, hospital and related services and benefits. This council is authorized to *advise* the Surgeon General. All physicians legally qualified by a state shall be qualified to furnish services; that is, if they wish to and are accepted by the Surgeon General. Every person may select his physician from those accepted by the Surgeon General, subject to the consent of the practitioner selected; that is, there is a free choice of physicians.

Specialists, however, shall be named by the Surgeon General, and their services shall "ordinarily be available only upon the advice of the general practitioner."

A fee schedule shall be set up by the Surgeon General, established on a per capita basis or a salary plan, or a combination of these — a provision that places great power in the hands of the Surgeon General. He may also limit the number of potential beneficiaries for whom a practitioner may undertake to furnish general medical benefits or distribute them, if the per capita plan is used, on a pro rata basis among practitioners. Thus he can control the amount of work any physician may do as regards this plan.

In a similar manner the Surgeon General shall select participating hospitals. The bill fixes the amount that may be paid for hospital services, to be "not less than \$3 and not more than \$6 per day for thirty days" and after that "not less than \$1.50 nor more than \$4." Payments are made to beneficiaries who, however, *may* assign their benefits to hospitals.

What are the general premises and principles involved? What are the underlying needs for such a bill? The Committee on the Costs of Medical Care pointed out that there are four groups of people. The first includes the rich or well to do, who have ample resources to meet the costs of medical and hospital care, with incomes of \$5000 and over. They form 9.2 per cent of the population. The second is the middle class, with incomes of \$2000 to \$5000, forming 35.5 per cent of the population. Voluntary plans have appealed to this group. Third comes the wage-earning group, with incomes from \$1000 to \$2000, forming 41 per cent of the population. Proponents of compulsory insurance believe that this class will never take out much voluntary insurance and must be compelled to protect itself through compulsory insurance. The fourth group comprises the indigent — persons with incomes below \$1000, forming 14 per cent of the population. Many of these are unemployable and will never be able to contribute adequately to any plan; they must be assisted by welfare and given medical and hospital care at public expense.

The difference of opinion regarding the third group is the crux of the matter. Proponents of compulsory insurance believe that these people will never take out much voluntary insurance and must be compelled to protect themselves and thereby the community, through compulsory insurance. Those favoring voluntary methods say that given adequate wages and time to acquaint themselves with the benefits of voluntary insurance and to understand it, this group will rise to the occasion. They cite the facts that most of the automobiles, electric refrigerators, radios, homes and furniture are bought on an installment plan, — that is, by budgeting, — and that people who voluntarily do this are also

bright enough to see the advantages of prepayment health insurance. They also point out that there is an advantage to the community in the development of personal initiative of this sort, of which more later. In rebuttal, the compulsory group says that this plan might work with high wages, but questions its effectiveness in periods of depression. So far as the wage-earners' contributions go, if they are out of work or are on mere subsistence wages neither plan will work, although the compulsory plan has advantages, since it includes the contribution of the employer and the possibility that the government will also assist through contributions from general taxation, thus gaining support from three sources instead of only one. It is well to remember, however, that all the money eventually comes from the taxpayer, be he rich or poor. There is validity to the arguments of both sides; it is a matter of relative values.

One of the principles of democratic government is that "the Government should do only those things that the people cannot do." Wendell Willkie said in his speech at the opening of the Greater Boston United War Fund campaign:

Totalitarianism has an insidious and sinister appeal — an appeal that is by no means limited to those nations where it is completely dominant. It appeals to those who prefer leadership to initiative, blueprints to enterprise, a blind following to freedom. It appeals to those who find it difficult to bend democracy to serve their economic or political self-interest.

The United States was founded on the principle of personal initiative and the participation of its citizens in the affairs and machinery of their government as well as in the prosecution of their livelihood or business. This country has been developed through personal enterprise and initiative, and I, for one, do not believe that the end of the possibilities of these factors has been reached. For instance, the people of Greater Boston pledged \$15,000,000 to the Greater Boston United War Fund in 1943 — a voluntary effort.

Civilization forces restrictions on the initiative and freedom of individuals, but these restrictions are accepted by all but the criminal class, voluntarily and with the understanding and belief that they are for the good of the community and, therefore, for their personal advantage. For example, taxation is a relinquishment of the freedom of spending one's own money as one wishes, as a result of which one obtains certain benefits from the states. Compulsory insurance is a form of taxation. In developing our form of government we have agreed that the Federal Government can do some things better than the states. These activities include the Army and Navy and the protection of the country, the control of currency through the Treasury and the Federal Reserve System, the carrying of mails through the Post Office Department, the Interstate Commerce Commission and the control of epidemics through the United States Public Health Service. It has also been agreed that states can do some

things better than cities. These activities include general laws affecting all residents of the states, the general direction of education, the licensing of doctors, lawyers and nurses, workmen's compensation laws, the care of tuberculous and mental patients (sanitation and state boards of health) and roads and other public works. Lastly, it is agreed that cities and towns can regulate best police and fire departments, local health and welfare matters, schools and local public works. This is all built on the sound principle that the larger unit shall take responsibility only for those things that it can do better than the smaller — and it should be remembered that it all begins with the individual citizen.

Of course there is a wide variation in what cities or states are willing to do. This gives an uneven distribution of public works, public service, regulating laws and so forth. Public works and service, although they offer benefits, cost money that must be raised by taxation. In general, those communities that have the greatest public services also have the highest tax rates. Those communities that want them must pay for them. Federalization of any project means that some communities will have to pay not only for the public services that they now have but also for similar services in communities that do not have them and are too poor or are unwilling to pay for them. It may be argued that it is just that the richer community should help the poorer, and that by its so doing the whole country is benefited and even the doubly taxed richer community receives adequate benefit through the improvement of its neighbor, but let us recognize what is going to take place.

So much for the state. Now what about the individual; how does taxation affect him? Everyone wants freedom and security: freedom of religion, of speech, of work and of spending; security through protection against want, loss of work and unemployment, provision for old age when earning power is lost, protection of dependents in the event of the death of the wage earner and protection against the cost of sickness and the accompanying loss of income.

Apparently, security can be reached only through the voluntary renunciation of some part of freedom. To achieve security for old age, unemployment and sickness, one must give up complete freedom of spending one's earnings. That is, one must pay for it through taxation or save for it oneself. The question is, How is one to do it? By initiative through savings, or by voluntary insurance, or by legislative enactment, through elected representatives, of compulsory insurance, which is taxation? So much for principles. Now let us take a practical view.

Evolution is terribly slow. Voluntary plans will take a long time; perhaps twenty years will be needed to accomplish what a legislative enactment could accomplish in two years. Many people will

suffer during this period from their own lack of foresight and from imperfect plans. There may always be some improvident people who will never protect themselves, who will spend their money willfully and then fall back on the community as indigents. Legislation is quick, albeit revolutionary. But, it may reasonably be asked, since we are progressing on the voluntary road, Is it necessary to rush things? After all, Rome was not built in a day. Compulsory insurance will apply to all who need it. It will make medical and hospital care available without direct cost at the time of sickness to all who need it, thus overcoming the unpredictable element in sickness as well as the uneven distribution of such care as is necessitated by limitation of income; that is, more people will get more care. It is urged that the loss of freedom and the cost through contributions are more than compensated by returns in benefits and security. A federal unified system will apply equally to all parts of the United States. Those areas with high tax rates can afford, on the basis of public good, to help the poorer areas. Universal benefit will result. What helps one's neighbor will in the long run help oneself. That is a good Christian doctrine, but what will be the cost?

According to the bill, which is based on statistics collected by the Bureau of Research and Statistics of the Social Security Board, the employee will pay to the unified system 6 per cent of his wages, and his employer will also pay 6 per cent of the pay roll. This applies to all wages up to \$3000 a year. Approximately one quarter of this total is set aside for medical and hospital benefits or, as it is commonly termed, "compulsory health insurance."

The following figures are only approximate and are not official; they will, however, help one to understand the workings of the plan. The estimated normal income of wage earners in the United States is \$100,000,000,000. Twelve per cent of this is \$12,000,000,000. Of this, one fourth, or 3 per cent of the total income, is to be set aside for medical and hospital care. Of this \$3,000,000,000, one third is to be set aside for hospital care, leaving \$2,000,000,000 for medical care. These figures may be too high, but granting a considerable shrinkage it appears that the statistical basis of the plan is reasonably sound and that certainly, so far as hospital costs are concerned, there would be enough money to pay the hospital bills.

How does this apply to the taxpayer? The population of the United States is approximately 120,000,000. The number of wage earners is 30,000,000 or one quarter of the population. With their dependents they total 80,000,000, or two thirds of the population. Take the case of a person earning \$2000 a year; 6 per cent of this is \$120, which will be his direct contribution or tax. But employers also pay 6 per cent, which in time will be added to the cost of production of every article, and so produce a rise in the cost of living for every one of the

120,000,000 persons in this country. The wage earner must eventually pay his share of this added cost for himself and his dependents, and since they form two thirds of the population, he will pay two thirds of this added cost of living, or 4 per cent of the employers' 6 per cent. Consequently, he will pay 6 per cent of his salary in direct taxes and 4 per cent in indirect taxes, or 10 per cent in all. Therefore, his real contribution will not be \$120 but \$200. In return for this he will get old-age pensions, unemployment payments, survivor benefits and medical and hospital care. In addition, he must pay his regular direct and indirect taxes to the federal, state and city governments. It is estimated that at present everyone is paying in one way or another between 25 and 30 per cent of his income in taxes. If this bill is passed he will be paying 35 to 40 per cent of his income. Is it not fair to ask how far this taxation, allocation or checkoff on wages can go and still permit the wage earner to maintain initiative and freedom? To be sure, he gets much in return, but one must ask, "What price freedom?"

It is true that this extra 10 per cent will not all be additional, since both employers and wage earners are already contributing to the Social Security Fund. Present social-insurance taxes are as follows: employers, 1 per cent for old-age pensions and survivor benefits and 3 per cent for unemployment compensation; and employees, 1 per cent for old-age pensions and survivor benefits. Thus the employers are paying 4 per cent of the suggested future 6 per cent, but the employees are paying only 1 per cent of it. Therefore, the employee will pay 5 per cent more as his own contribution, plus two thirds of the 2 per cent increase in employers' tax, or a total of 5 per cent plus $1\frac{1}{3}$ per cent, or $6\frac{1}{3}$ per cent more from his wages than he is now paying.

It is also true that the Social Security Act calls for increases to 2 per cent on January 1, 1944, for both employer and employee to cover old-age and survivor benefits, to $2\frac{1}{2}$ per cent in 1946, and to 3 per cent in 1949. Nevertheless, the point is still pertinent that there will be a substantial increase in taxes taken directly from wages.

The experience of all European plans, of voluntary plans in this country and of university departments of hygiene where students pay a fixed health fee, is that the amount of medical care is increased. Human nature is such that, having contributed, everyone wants to receive some benefit. Granted that more medical care than is now utilized is desirable, it will be well to consider whether the existing number of physicians, nurses and hospitals will be able to meet the demands that will suddenly be thrust on them. This is not an argument against providing more medical and hospital care but rather against a too rapid change from one system to another. After all, medical care is dependent on individual doctors, and hospital care is limited by the extent of hospital facilities. If the amount of

care is to be increased, so must the means of providing it. Promises that cannot be fulfilled lead to exasperation of those who are disappointed. Some check that will control too rapid expansion seems to be indicated.

* * *

If we believe that our present medical and hospital system is satisfactory, that it is developing adequate methods of meeting economic needs, and that it will in a reasonable time supply adequate medical and hospital care to all at costs and by methods within their means, we should oppose the Wagner-Murray-Dingell Bill. If we believe that the present system is unsatisfactory and inadequate and that voluntary plans will never adequately provide medical and hospital care, that the third group outlined above, comprising 41 per cent of the population, will never be satisfactorily protected, we must decide whether we shall achieve this protection through direct general taxation or through compulsory insurance. Between these two choices there is no doubt that compulsory insurance is the better plan. If we decide to have compulsory insurance we may support the Wagner-Murray-Dingell Bill, but, it is to be hoped, with certain important changes. Let us for the sake of argument take the stand that compulsory health insurance is desirable and consider how it would operate under the provisions of this bill.

First of all, there is the problem of federalization of the medical and hospital system; for although the plan begins with qualification of physicians and hospitals by states, if this bill passes it is only a question of time before qualification will become a federal power. Although I deplore in general the concentration of power in federal bureaus, I cannot see anything reprehensible in the federal licensing of physicians and hospitals. I can, however, see great difficulties in centralized bureaus' appreciating and understanding local conditions. There will inevitably be a tendency to set up rules and regulations and to apply them universally, with the result that what is applicable with advantage to conditions in one state may be disadvantageous when applied to different conditions in another state. I can also foresee great possibilities for pressure groups and logrolling deals, since local communities will thereby stand to obtain great benefits at small cost to themselves; witness the efforts to obtain veterans' hospitals.

Without question, the authority granted to the Surgeon General of the Public Health System is too great. Granting the integrity and ability of Surgeon General Parran, and those who have preceded him and will follow him, the concentration in one man of the power to select or reject the physicians and designate or reject the hospitals that may participate in this plan approaches dictatorial powers. May he not under pressure in turn use pressure on these

appointees to influence them in their activities, both social and medical, with loss of appointment as the result of nonconformity?

It seems obvious that there must be nonpartisan control of such power. This could be made possible by changing the suggested advisory committee to a directing committee, which would have the authority to determine policies and principles and to direct the Surgeon General and review his acts, and to which he must report. This committee should not be selected by him but should be composed of representatives selected by those national organizations most competent to judge the quality and quantity of medical and hospital care, and most interested in the successful operation of this project. Such a change would adhere to the well-known principle of organization of having a policy-making body, with an executive to carry out its policies and to report to it. This is the organization of the Government: Congress makes the laws; the President carries them out. It is the organization of corporations: the board of directors makes the policies; the general manager executes them. The Surgeon General of the Public Health Service is the logical executive officer to administer the regulations of such a directing committee. He should not be the chairman.

With control placed in the hands of a directing committee composed of physicians, hospital administrators, dentists, nurses and lay representatives of other interested organizations, many of the controversial subjects in this bill could be cared for; for instance, the method of payment, — whether by fee schedule, a panel per capita plan, or by salary, — and the selection of physicians, the designation of specialists, the acceptance of hospitals and the adequacy of payment for hospital service, since the decision on these matters would be placed in the hands of those who would know the facts and understand the conditions and who would be interested in the success of the undertaking. The acquisition and probable misuse of power would be avoided so far as possible. Nor would the effectiveness of administration by the Surgeon General be prevented, because he would be given free scope to carry out the provisions laid down for him.

The next point is one of omission in the bill. The present hospital system has been successfully built on the general principle of government co-operation and supplementation instead of replacement. Government hospitals — federal, state and municipal — co-operate with and supplement non-governmental or voluntary hospitals in providing care. Furthermore, this system promotes friendly but active competition in producing better care of patients. There should be added to the bill the proviso that membership in a voluntary hospital or medical-insurance plan that provides comparable benefits is acceptable in lieu of compulsory contributions. Compulsory insurance may be required

for others. Admittedly this lays a heavy burden on the voluntary plans, because compulsory plans have the advantage of forced payments from employers. But voluntary plans have the advantage of working under flat rates, which makes them attractive to those earning higher wages. Certainly such a proposition will stimulate competition to see which plan can produce the best results. To compete, the Blue Cross must operate in all states with reciprocity, and the Blue Shield will have to develop rapidly more nearly complete medical benefits. Moreover, — and this is extremely important, — such a provision would adhere to the American principle of encouraging personal initiative and of encouraging thinking and choice on the part of every wage earner. Thereby he becomes a better citizen.

For this bill to be acceptable to most people it must present a rational plan clearly defining how the central regulating federal organization can be decentralized to administer benefits and to adjust general principles and policies to local conditions. Shall this be done by existing state organizations or shall a new board, composed of representatives of all the present state departments involved, with perhaps additions representing interested groups, be set up? A substantial amount of local administration must be guaranteed.

Lastly, it is essential that payments for medical and hospital service be made directly to the physician and hospital and not to the subscriber beneficiary. Only in this way can payment for service be assured. The present permissive statement that beneficiaries may assign payments is not satisfactory.

If legislation is to be enacted it should adhere to certain basic principles: It should disrupt present conditions as little as possible. Therefore, legislation for compulsory health insurance should assist, co-operate with and supplement the present medical and hospital system — not replace it. This means that the principle of private medical practice and voluntary hospital and medical insurance plans shall be specifically recognized and their existence approved. Second, the bill should permit opportunity of choice; that is, the citizen should have a choice between joining a voluntary medical and hospital insurance plan providing comparable protection and accepting compulsory insurance. In other words, membership in a voluntary plan providing comparable benefits should be accepted in lieu of compulsory insurance. Third, the bill should permit the operation on a local basis, through state

organization, of principles and policies developed on a federal basis. In other words, there should be federal guidance and control but local application. In no other way can local conditions and variation be successfully understood and met. Fourth, the bill should place control of any health plan in the hands of those most interested and best informed concerning the quality and quantity of medical and hospital care. To this end a governing or directing committee, composed of physicians, hospital administrators, dentists, nurses, public-health officials and others representing the public, should be created to develop policies and principles to be carried out by their agent, who may properly be the Surgeon General of the United States Public Health Service. Lastly, the objective of such legislation should be to provide medical and hospital service not to provide a cash payment that might be used to obtain medical and hospital care. To achieve this, payments for service should be made directly to the physician or hospital and not to the beneficiary.

If these principles are adhered to, it is safe to present a plan of compulsory health insurance to the people of this country for consideration, for under these conditions freedom of choice and of action is still theirs.

* * *

In conclusion, since I am at heart an individualist since I think that government best that governs least, and since I think that evolution is the safe way to advance, I am emotionally in favor of voluntary insurance and against compulsory plan. Perhaps these emotions are but the conscious components or results of experience. At the same time I cannot find any convincing logical argument against the general principles of compulsory plan only criticism of specific points and a difference of opinion concerning the desirability of doing things that way. Therefore, from the standpoint of reason and logic I cannot honestly oppose the idea of compulsory plans.

There is so much to be said on both sides that perhaps the answer is that each side may be partly right and that the only way to find the truth is through a fair trial. Why not, then, accept a trial of compulsory health insurance, being careful that it does not replace free enterprise in the shape of voluntary insurance, but that it is operated as a co-operative, supplementary plan, with as few undesirable complications of operation as possible. In other words, if there must be compulsory insurance, let this bill be made as nearly perfect as possible through constructive criticism.

PROLONGED CASES OF GRIEF REACTION TREATED BY ELECTRIC SHOCK

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THE 4 cases that are here reported in somewhat disguised form are technically classified under the heading "reactive depressions." In each of these cases, however, the immediate precipitating factor was the loss by sudden death of someone close and dear to the patient, so that the term "grief reaction"† has been used to designate the mental state of the patient. Electric-shock therapy was used with such excellent results as to merit their publication.

CASE REPORTS

CASE 1. A 48-year-old, married woman had all her life exercised obsessive scrupulosity — that is, a tendency to examine her own acts under over-rigid criteria of right and wrong. With it she was the victim of what may properly be called excessive religiosity, in that she was constantly praying for guidance under circumstances that would not seem to the ordinary religious person to demand such fervency. She was, however, active and well and without any overt mental disturbance until shortly after her only son died under tragic accidental circumstances. The grief reaction was immediate, and she became obsessed with the idea that she was somehow to blame. The train of so-called "reasoning" was circuitous, and the train of guilt was extreme, and the appeals, in other words, were mingled with derisive and even obscene thoughts. For example, the word "God" became linked with the word "dog," to the horror of her helpless mind. She developed rituals by which she sought to prevent God from taking vengeance on her for her blasphemous reactions. She became sleepless and emaciated, and the psychosis evolved steadily toward an increasing, agitated depression, with obsessive thoughts and compulsive acts. At no time did she lose insight, since she realized that her state of mind was pathologic.

Psychotherapy was attempted by a colleague of high standing, with no results. Drugs were used, mainly sedatives, together with amphetamine sulfate, hormones, vitamins and so forth, but the psychosis increased in severity despite these forms of treatment. Electric-shock treatment was finally decided on, and the patient had to be forced into taking it. Three shocks were given at her home. At the end of the third she begged to have the treatment stopped, stating that she felt much better and that the obsessive and grief-stricken thoughts were "far away." Her appeal was granted, and she steadily continued to improve. Mild sedatives were then sufficient to maintain her improvement. A few months after the shock treatment was stopped.

The patient has continued to remain well. The grief reaction is still present but in a rational form. The obsessive and compulsive reactions have disappeared and she is in normal condition.

CASE 2. A 52-year-old, married woman with a previous history of moderately neurasthenic reactions had always been dependent on her husband for decisions of major importance and entirely wrapped up in her domestic affairs. In June, 1939, her husband, a distinguished engineer, suddenly died of coronary thrombosis. On his death it was discovered that his affairs were in an extremely tangled state. He had been lavish in his help to others, but left no legal papers that indicated the amounts he had given nor the circumstances

under which the loans were to be repaid. Thus, the estate consisted of a small amount of insurance and a large amount of dubiously collectible loans and gifts.

Almost immediately the widow plunged into a severe depressive reaction, and was constantly preoccupied with the injustice and ungratefulness of those who had been the objects of her husband's benevolence. Against her own will she had a bitter and disloyal resentment against her husband, partly because he had not taken her into his confidence, but mainly because of the carelessness with which he had kept his accounts. She became sleepless, lost weight, was constantly agitated over the situation, and reiterated her feelings of doubt and helplessness. She was unable to do her housework and could make no plans for the future. There were no delusions. As a matter of fact, whatever she stated about her husband's financial affairs was entirely true, since a survey of his accounts and his checkbooks showed an appalling lack of discretion in the way his money had flowed into the pockets of others.

Psychotherapeutics, a change of scene, sedatives, hormones and finally a prolonged stay in an institution for the treatment of mental disease were equally unavailing, and after nearly four years the condition remained practically unchanged. Doubt, indecision, depression, agitation, impairment of the appetite and inability to sleep or to carry on her life in any co-ordinated, organized way were still present and continuously expressed, to the complete distraction of the patient, and the demoralization of her family.

On September 1, 1942, outpatient electric-shock treatment was begun, almost against the patient's will, since she could in no way decide what to do. Ten treatments were given in rapid succession. Little improvement was noted, and

even know she was a widow, and had no memory of the facts and names of people with whom she had been on intimate terms throughout her life, although she could recognize her son and a few closely related persons. She did not remember her illness, and the last five years of her life were practically wiped out. During the next 3 weeks gradually her memory returned. She recalled her husband's death, and commenced to recognize that she had been sick and to realize the nature of her abnormal response. Sleep became normal, and the appetite was restored in adequate measure; at the end of 6 weeks she recommenced her housework, and in the course of the next month she was reading newspapers, listening to the radio, visiting friends and carrying on her duties as mother and housekeeper about as well as ever before. She was greatly concerned about the money that had, as she put it, "disappeared into the pockets of others," but for the first time she was able to take intelligent and adequate measures for the recovery of the lost funds, and in fact showed considerable intelligence and business judgment in dealing with her affairs.

She has reported from time to time during the year since the shock treatment was discontinued. Although she is still a neurasthenic type of person, complaining from time to time of various pains and aches, — digestive disturbances and the like, — she has maintained a well-organized mental life and is substantially well.

CASE 3. A 48-year-old, married woman carried on an active life in her community, was a musician, and was devoted to her husband and two children. The former was killed in an accident. The patient felt as though she had "no prop left" in her life. Immediately she fell into a state of depression, with self-accusation on the slender ground that she had not prevented her husband from working too hard and thus subjecting himself to unnecessary risks. She became entirely sleepless, lost her appetite completely, and complained of burning feelings throughout her body, and manifested an inability to make decisions in any minor

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†To my knowledge, this term was first used by Cobb and Lindemann.

affairs. Finally she made a desperate attempt at suicide and was sent to a state institution, where she remained for a month. She was then discharged, against advice, with a diagnosis of reactive depression. During her stay she had been appalled by her incarceration and the manifestations of insanity by other patients. She sequestered herself in her home for nearly a year following her discharge. She had no desire for any of the pleasures of life — what I² have elsewhere called "anhedonia" — and felt that the world was unreal and without any worth and that living was an almost intolerable burden. She could not even summon up interest in the affairs of her sons, who were in the Army. This brooding state remained unaltered for months, and, as the patient phrased it, she had felt "like a ghost" ever since her husband died.

Finally, in January, 1943, outpatient electric-shock treatments were given, five in number on alternate days. The improvement was marked from the third shock on. At the end of the series the patient slept well, had regained her normal appetite, smiled and laughed naturally, and was willing to take up her affairs again. She went back to her music, became absorbed in the care of her house, corresponded affectionately with her sons, and in a short time was reacting entirely normally to the death of her husband and to her status as a widow.

CASE 4. A 28-year-old, married woman was first seen on May 27, 1943, 6 months after the onset of her illness. She was intelligent, keen, active and social minded. Owing to the shortage of maids, she had to stay home each night with her baby, frequently alone. On one occasion she left the infant for an hour to visit a friend, and came home to find that he had suffocated in his crib. The grief reaction was extreme and was immediately associated with bitter self-accusation. Nothing would console her. She finally came to Boston from a distant city and placed herself under the care of a group of distinguished psychiatrists, who utilized psychotherapy but without avail.

On May 28 and 30, I administered electric-shock therapy. When she recovered from the unconsciousness and stupor of the first treatment, she felt peaceful and said that she had not been in so desirable a state of mind for many months. At the end of the second shock she felt entirely well, and as a consequence no further treatments were administered.

She returned to her home and resumed her domestic duties.

DISCUSSION

Each of these cases, all of which significantly occurred in women, was characterized by an intense and prolonged grief reaction following a tragic bereavement. These reactions were to some degree warranted. The prolongation, intensity and transformation of the grief are its pathological features. All the patients fell into a vicious circle of nervous and mental disturbance from which it seemed impossible to rescue them by the ordinary therapeutic measures. Just how the electric-shock method operated in these cases is a theme for fertile speculation, without, however, any basis of established facts. In Case 2 the abnormal mental state had persisted for years, and it was necessary to produce an amentia — that is, to wipe out for a time almost all memory — before the personality could reorganize itself along normal lines. In the other 3 cases a few electric shocks brought about striking and immediate improvement and recovery. It does not therefore seem necessary to erase the memory of the traumatic experience to produce a readjustment to the altered life that bereavement has brought in its train. The value of shock treatment does not appear to have a psychologic foundation. Rather, physiologic alterations of an unknown type take place, and this is the basis of the recovery.

475 Commonwealth Avenue

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MEDICAL PROGRESS

CARDIOGENIC SHOCK (Concluded)*

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BOSTON

ORIAS²⁸ studied the dynamic changes in the ventricles following experimental coronary occlusion and offered a reasonable, and probably important, explanation for the changes observed. In general, three types of responses were encountered. In a few animals the aortic and left-ventricular pressures fell progressively with evidence of cardiac dilatation and failure. In another group of animals there was an immediate fall in aortic and left-ventricular pressure, followed quickly by recovery of the cardiodynamics to the preligation level. A small group of animals showed no fall in pressure, and in them the only evidence of altered dynamics

was a decrease in the ejection phase, an alteration that was also observed in the other groups. Orias interpreted these responses as indicating that deflection of a portion of the ventricular muscle immediately resulted in a hypodynamic beat and consequent dilatation of the heart. If the nonischemic muscle was able to respond normally to the increased diastolic size, it compensated for the loss of the ischemic area and the dynamics returned to normal. If the nonischemic muscle could not respond with increased vigor of contraction, in accordance with Starling's law, progressive heart failure and a falling blood pressure appeared. This may well explain why a fall in blood pressure has not been a striking feature of experimental coronary occlusion, for in the majority of such experiments the blood supply and

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the cardiac reserve of the uninfarcted regions were essentially normal. Unfortunately, this does not obtain in many patients with coronary occlusion because of the presence of generalized coronary artery disease or because of the loss of cardiac reserve incident to chronic hypertension. Obviously, the amount of uninfarcted muscle remaining, as well as its condition, is an important factor in the ability of the heart to compensate. Thus the hope of compensation in a heart subject to depletion of a large portion of its muscle mass is slim.

Even if Orias's concept is fundamentally correct, — and no better one has yet been offered, — it is still conceivable that peripheral mechanisms play a contributory role. Two possibilities present themselves. First, primary or neurogenic shock may occur at the onset of the attack, and the resultant fall in blood pressure may so diminish blood flow in the unoccluded coronary arteries as to depress the uninfarcted muscle, thus preventing its normal compensatory response. The result would then be progressive hypodynamic heart action and shock persisting beyond the usual duration of primary shock. That such a train of events may occur cannot be gainsaid, but the force of the contention is somewhat weakened by the fact that in occasional cases the onset of the attack is marked by an increase in blood pressure that may later give way to shock. Such a series of events is unusual because the mere ability of the heart to sustain a blood pressure higher than preinfarction levels attests to its ability to compensate fully. In the rare cases in which it does occur, other collateral factors may possibly play a role.

The second possibility is concerned with whether true peripheral shock may not ultimately appear following a prolonged period of capillary anoxia secondary to cardiogenic shock. It is well known that large doses of epinephrine given over a long period of time may give rise to shock, and that intermittent obstruction to the arterial or venous blood flow to an extremity may do the same. Furthermore, it has recently been shown²⁹ that sustained hypotension induced by continuous stimulation of the carotid sinus may induce the clinical and pathologic picture of traumatic shock. Against such a contention is the fact that no significant decrease in circulating blood volume or hemoconcentration has been demonstrated in myocardial infarction accompanied by shock, although studies of this kind have not been correlated with the duration of the shock. A more potent argument against such a concept is the fact that the state of shock induced by prolonged anoxia is largely an irreversible process and that recovery is rare. This is not necessarily true in myocardial infarction, for patients may remain in shock for hours or even a day or two, yet ultimately recover.

It appears, therefore, that the bulk of evidence, both direct and theoretical, is overwhelmingly in

favor of the concept that shock in myocardial infarction is largely, and probably solely, a manifestation of heart failure.

Some therapeutic considerations can be adduced from the crystallization of present knowledge concerning shock in myocardial infarction. Since the evidence is opposed to any lack of circulating blood volume or loss of effective filling pressure of the left ventricle, measures adopted to combat traumatic shock, such as the use of intravenous fluids or blood, are not only uncalled for but are, of course, contraindicated. Conversely, the reduction of the circulating-blood volume is not contraindicated so long as the evidence indicates an adequate supply of blood to the left side of the heart. The combination of shock and pulmonary edema is not unusual, and in such cases there has been a reluctance to bleed the patient because of the possibility of aggravating the shock. Since pulmonary edema is a manifestation of high pressure in the pulmonary veins, it follows that more than adequate blood is available to the left side of the heart, and no hesitancy need be felt in venesectioning such patients. Indeed, pulmonary edema may constitute a more immediate threat to life than does shock, and venesection may occasionally be lifesaving. Stead and Ebert³ withdrew 650 and 500 cc. of blood, respectively, from two patients with myocardial infarction and shock without any evident harmful effects.

Unless the reasoning has been false, measures designed to combat shock in myocardial infarction should be mainly directed toward supporting the uninfarcted muscle. Some attention has been given to the subject of treatment of this form of shock, but it has not received the consideration it deserves, probably owing to the contention of some clinicians that a low blood pressure relieves the work of the heart and therefore should not be vigorously combated. It should not be inferred that moderate reduction of blood pressure should be attacked vigorously, but it is hardly conceivable that a state of profound shock is helpful to the bodily economy.

The intravenous injection of 50 per cent glucose solution has been recommended by some authors for the treatment of shock in myocardial infarction, and success with this method has been reported. I have never seen recovery from shock attributable to this procedure, and many clinicians have had a similar experience. Furthermore, there is no evidence that the blood volume needs to be supplemented, nor is there evidence that the heart lacks fuel to burn — the two main attributes of hypertonic glucose solution.

Oxygen therapy has been found useful in the treatment of shock in myocardial infarction. The rationale of its use is not to increase the oxygen supply to the infarcted tissue, for it is probable that no available measure can immediately increase the blood or oxygen supply to this area.³⁰ Its usefulness

lies in increasing the oxygen available to the uninfarcted muscle, hence enhancing its ability to compensate. Even the small amounts of additional oxygen that can be taken up by normally saturated blood may serve a useful purpose. It is probable, however, that at times, owing to pulmonary congestion, the blood is not normally saturated. Under such circumstances, oxygen administration fulfills an important service.

The experimental work of Manning, McEachern and Hall³¹ and LeRoy and Snider³² indicates that sudden occlusion of one coronary branch leads to reflex constriction of other coronary arteries. If such a phenomenon occurs in human beings, it must constitute a significant barrier to an adequate response of the uninfarcted muscle. The drugs that have been recommended for overcoming this reflex constriction are atropine, aminophylline and papaverine. In addition, aminophylline is a myocardial stimulant and may be temporarily useful for this reason alone.^{33, 34} Also, papaverine has been found to decrease ventricular irritability,^{35, 36} and its use may reduce the danger of ventricular ectopic rhythm. None of these drugs have been adequately evaluated for their effect on shock in myocardial infarction, and their inclusion here is based on theoretical grounds alone.

If one accepts shock in myocardial infarction as a manifestation of heart failure, the use of digitalis and other cardiac glycosides must come in for very serious consideration. In general, the use of digitalis has been avoided during the acute stages of the disease, for the following reasons. First, it decreases cardiac output in patients without heart failure, and it has been thought that this effect may aggravate the shock. Since the evidence favors the presence of congestive heart failure in myocardial infarction, even in patients who show predominant signs of shock, it is apparent that this objection is insignificant and may be disregarded. Second, the use of digitalis has been objected to on the ground that stimulation of the heart may increase the danger of cardiac rupture. Undoubtedly this objection has been overrated, particularly so in the present connection since the appearance of shock is usually limited to the first day or two, a time when ventricular rupture is unlikely. Moreover, digitalis has commonly been used to combat congestive heart failure in the later stages of cardiac infarction, when rupture is more likely to occur, without evidence of undue prevalence of this complication. Finally, the objection has been raised that digitalis increases ventricular irritability and increases the likelihood of fatal ventricular fibrillation. Although this objection is possibly valid, it should be recalled that such ventricular irritability is usually to be attributed to excessive amounts of digitalis. It has not been demonstrated that cardiac infarction sensitizes the heart to therapeutic amounts of the drug.

It has been shown that in the experimental animal digitalis does not significantly alter the fibrillation threshold of the ventricles.³⁷ It has also been demonstrated that the spontaneous ventricular fibrillation that occurs with toxic amounts of digitalis differs in several particulars from that which occurs with coronary occlusion.^{37, 38} Although myocardial ischemia lowers the fibrillation threshold, it has not been shown that this increases the tendency of digitalis to produce fibrillation. Indeed, there is considerable evidence that this is not true.

In 1925, Gold³⁹ found that the lethal dose of ouabain for cats subjected to coronary artery ligation did not differ from that for normal animals. This study extended over a period of twenty-four hours following ligation. More recently, these findings were confirmed by Bellet, Johnston and Schecter,⁴⁰ but the latter authors extended the period of observation and found that four days following ligation the tolerance to digitalis diminished by 23 per cent of normal. Still later, Travell, Gold and Modell⁴¹ reported that the tolerance of cats to digitalis three weeks after ligation of the coronary arteries was diminished by 25 per cent. Since shock in cardiac infarction is usually an early manifestation, it appears from these experiments that no great fear need be felt in the use of digitalis. Furthermore, as emphasized by Travell, Gold and Modell, all these studies have been concerned with lethal amounts of the drug, and no information concerning therapeutic amounts of the drug has been forthcoming. They conclude that the results lend no support to the belief that the use of digitalis is attended by any special hazards in these cases [coronary occlusion].

Certainly digitalis has been used in many patients with acute myocardial infarction accompanied by congestive heart failure. The number of sudden deaths in such patients is probably no larger than might be expected in a similar group not receiving digitalis. Stead and Ebert⁵ gave intravenous strophanthin to 2 patients in shock with myocardial infarction without evidence of benefit or harm. The number is, of course, too small to evaluate the possible hazards or benefits of this drug, but it indicates that digitalis bodies can be given under such circumstances without invariably producing disastrous results.

Strophanthin or ouabain is probably the drug of choice, since its action is rapid, it does not accumulate so readily as digitalis, and it is said to have a greater direct action on the myocardium than does digitalis.⁴²

It should not be supposed that digitalis bodies are being enthusiastically recommended for the treatment of shock in myocardial infarction. There is no assurance that they do good nor that they are entirely free of danger. The suggestion is simply made that, on theoretical grounds, such substances

may be expected to turn the scales in some cases, and that objections to their use have probably been greatly overemphasized.

The subject of therapy should not be left without some discussion of the use of pressor drugs. A few physicians have used epinephrine unhesitatingly in shock associated with myocardial infarction, some have been goaded into its use by the necessity of desperate circumstances, and some have avoided it completely. Several objections have been raised to its use. It has been thought to be contraindicated in all forms of shock because arteriolar constriction is already present, and if epinephrine does succeed in producing further constriction it will only serve to increase capillary anoxia and thus aggravate the shock. This may apply to traumatic shock, but it is probably insignificant in the type of shock under discussion.

Pressor drugs have also been objected to on the ground that hypotension relieves the work of the heart and is a compensatory mechanism, and hence should not be combated. This is not an especially appealing argument. Inasmuch as the ability of the uninfarcted muscle to compensate is determined, in large part, by its blood supply, which, in turn, is determined largely by the aortic blood pressure, it seems desirable to overcome a profound fall in blood pressure if possible. The opposing argument could only be considered valid if it could be shown that the decrease in cardiac work associated with shock is disproportionately greater than the decrease in coronary blood flow. This seems extremely unlikely.

Epinephrine has also been objected to on the ground that it tends to produce ventricular irritability. This belief has some support in clinical and experimental observations, but recent work indicates that the ventricles of experimental animals are more resistant to the production of ventricular fibrillation after the administration of epinephrine than they are in the untreated state.³⁵ It should also be recalled that in patients with Adams-Stokes's attacks complicating acute myocardial infarction, epinephrine has been used repeatedly and in large amounts with nothing but benefit resulting in the majority of cases.

Meek³⁴ has recently reviewed the evidence relative to the production of ventricular tachycardia by epinephrine, especially in regard to its effect during cyclopropane, chloroform and ether anesthesia. Several interesting observations pertinent to the present discussion have been made. Under the conditions of the reported experiments, it was demonstrated that, especially with cyclopropane, epinephrine produced ventricular tachycardia regularly, whereas similar doses in the unanesthetized dog produced it but rarely. It was also demonstrated that sensitization of the heart itself by cyclopropane is of much less importance than nervous impulses reaching the heart by way of the sympathetic pathways. It is possible, therefore, that the combined

effect of cyclopropane and epinephrine is simply equivalent to the effect of a large dose of epinephrine alone. In any event, the analogy of sensitization of the heart by anesthetic agents and the possible sensitization by coronary occlusion may not be very close, and is certainly not established. Meek also noted that other amines were as effective as adrenalin in producing ventricular tachycardia under cyclopropane anesthesia, and that only amines with a catechol ring had this ability. To be effective, the various side chains in the structural formula must be attached to the 3-4-dihydroxy ring. Other drugs capable of producing the same degree of blood pressure increase but without the characteristic structural formula did not induce ventricular tachycardia. Such drugs were Ephedrine, Amphetamine (Benzedrine), Paredrine, Synephrine and Neo-Synephrine. It seems, therefore, that if pressor substances are to be used in myocardial infarction, one of the latter group is preferable to epinephrine.

A more important objection to epinephrine is its tendency to increase both the general and the cardiac metabolism. This effect is doubtlessly out of proportion to the increase in blood flow incident to its use, and the administration of epinephrine is therefore an uneconomical and probably unsafe procedure.⁴⁴ Ephedrine is an equally good, if not a better, pressor drug, and its tendency to stimulate metabolism is somewhat less than that of epinephrine.³³ Hence it is superior to epinephrine on at least two counts and perhaps deserves a place in the management of shock with myocardial infarction. Some of the newer sympathomimetic amines may prove to be superior, for one reason or another, to ephedrine.

* * *

It is fully realized that certain of the ideas expressed in this section devoted to myocardial infarction will be new to many readers and perhaps unacceptable to some. The ideas relating to treatment, especially, are not expressed as established facts, but an attempt has been made to assemble recent developments and to indicate the need for critical re-examination of older beliefs. It should again be emphasized that many questions are still unanswered, and that until more information is available on controversial points, trial of the unorthodox procedures should properly be limited to gravely ill patients whose prognosis has heretofore been almost universally bad. It should also be emphasized that, irrespective of the soundness of these therapeutic suggestions, many such cases are hopeless from the beginning because of the large size of the cardiac infarct and the paucity of remaining uninfarcted muscle.

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CASE RECORDS OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**BENJAMIN CASTLEMAN, M.D., *Acting Editor*EDITH E. PARRIS, *Assistant Editor*

CASE 30091

PRESENTATION OF CASE

A sixty-five-year-old man was admitted to the hospital with a compound fracture of the right leg incurred a few hours previously after a fall down a flight of stairs.

For about ten years prior to admission the patient had been treated in the Out Patient Department for pernicious anemia with parenteral liver extract. In spite of this therapy the hemoglobin and red-cell count had been falling over a period of a year. He had occasionally noted paresthesia in his feet and muscle cramp, with some difficulty in walking. He had dyspnea on exertion. His diet was poor, and he had been drinking 6 to 10 glasses of beer daily for many years. For three years the liver had been palpable.

Physical examination revealed a well-developed, well-nourished man who appeared drowsy. The tongue was red and beefy. A few rhonchi were audible at the right base. The heart was negative. The liver edge was palpable 3 cm. below the right costal margin. The left ankle jerk was absent, but the vibration and position senses seemed intact. The right leg revealed a compound comminuted fracture of the right tibia and fibula.

The temperature was 99.4°F., the pulse 132, and the respirations 16. The blood pressure was 160 systolic, 95 diastolic.

Examination of the blood showed a red-cell count of 3,920,000, with 65 per cent hemoglobin. The white-cell count was 8800, with 80 per cent neutrophils. There were no red-cell abnormalities. A urine examination was negative. The van den Bergh, blood nonprotein nitrogen, and blood protein determinations were normal. The albumin-globulin ratio was 3.0. The prothrombin time was 35 seconds (normal, 22 seconds). A blood Hinton test was negative.

The patient was immediately taken to the operating room, where a débridement, irrigation, open reduction and application of a Lane plate to the tibia were performed. A cast was applied and the patient was transfused and given sulfadiazine, which was discontinued after four days because of a fall in the white count to 4400. The temperature rose to 101

or 102°F. following the operation. An x-ray film of the chest during this period revealed prominence of the lung markings, especially at the right base. On the third postoperative day the temperature became normal, and remained so for two weeks, during which time the patient was asymptomatic. On the eighteenth hospital day, following a transfusion, the patient had a chill with a rise in temperature to 101°F., which continued for several days. The patient felt tired, and his appetite was poor. There was questionable tenderness over the left kidney, but the urine was negative. The lungs were clear. Two days later the cast was removed. The wound was well healed except for a small area over the fracture site, from which serosanguineous fluid exuded. This area soon sloughed, leaving a small portion of the plate exposed, but there was no evidence of extending infection.

Following a few days of normal temperature, it again rose, going to 100 or 101°F. daily. The patient remained lethargic. His appetite was poor, and he complained of cramplike abdominal pain and malaise. There was soreness in the epigastrium to the right of the midline. He also developed tenderness of the right calf, associated with edema of the foot, and a bilateral femoral-vein ligation was subsequently performed, without apparent change in his condition.

Although microscopical examination of the urine was essentially negative, urine culture revealed a moderate number of colonies of *Staphylococcus albus*. Because of this, together with the persistently elevated temperature, the patient was given small doses of sulfathiazole for a period of about two weeks, during which time there were only occasional rises in temperature to 100°F. The white-cell count ranged from 4000 to 7000, with 49 to 76 per cent neutrophils. Because of inadequate caloric intake and increasing evidences of dehydration and malnutrition, large amounts of vitamins as well as parenteral fluid and glucose were given. Administration of vitamin K (Hykinone) parenterally did not bring down the prothrombin time, which eventually reached 52 seconds (normal, 22 seconds). The blood protein was 8.9 gm. per 100 cc., with an albumin-globulin ratio of 0.5. The van den Bergh test remained normal. A cephalin flocculation test was +, but later ++. A bromsulfalein test revealed 35 per cent retention of the dye. Blood cultures were negative.

The patient's condition gradually deteriorated. The temperature spiked to 103 and 104°F. daily, and he had several chills. Examination revealed an emaciated man with a Parkinsonian rigidity and masklike facies. Crackling rales were audible at both bases, being more marked on the left. The heart was slightly enlarged, with soft systolic murmurs at the base and apex and an early diastolic apical gallop rhythm. The blood pressure was 108 systolic, 68 diastolic. The liver and the tip of the

*On leave of absence.

spleen were palpable. Some brawny ankle edema was present. A portable roentgenogram of the chest revealed poorly outlined mottled areas of increased density scattered throughout both lung fields.

On the seventy-second hospital day the patient developed considerable respiratory distress and became totally disoriented. He was placed in an oxygen tent but expired two days later.

DIFFERENTIAL DIAGNOSIS

DR. JACOB LERMAN: There are several interesting points that we should review and comment on before discussing the diagnosis. This man apparently had adequate parenteral therapy for pernicious anemia and then began to lose ground. Usually one of several factors explains the failure to respond or the tendency to relapse. Either the therapy is inadequate or subminimal, so that gradually the patient slips into a relapse, or infection or some toxic agent supervenes, or another degenerative disease develops. In this particular patient several factors existed. His diet was poor, he had been taking alcohol, and he had signs suggesting liver damage. All three factors might play a role in the failure to maintain a good response or in a tendency to relapse. The tendency to relapse is confirmed by the fact that he had a red, beefy tongue and weakness. Although there is a suggestion that he might have had combined-system disease, the presence of vibration and position senses is strongly against that possibility. The blood picture is that of mild anemia — he had not maintained his normal red count and hemoglobin. The increased prothrombin time is further evidence of liver damage. It is true that such an increase can be due to inadequate intake of vitamin K, but we learn later that vitamin K administration did not help.

The patient was operated on, and given sulfadiazine until leukopenia developed. On the eighteenth postoperative day there was a transfusion reaction. This raises the question whether the reaction could have been due to antibodies against the Rh factor. It is possible but one hardly expects a reaction to the Rh factor on the second transfusion, since it usually takes several transfusions to produce such a reaction.

There is a note that the patient was beginning to have renal pain. We know that in pernicious anemia, particularly in those cases associated with combined-system disease, kidney infection is of common occurrence. So our attention is drawn to the possibility of pyelitis, pyelonephritis or abscess involving the kidney or perirenal tissues. Further evidence of urinary infection is offered by the positive urine culture. The service apparently gave sulfonamides in an attempt to reduce the infection; it was partly successful but did not result in a cure.

The fever, lethargy, abdominal cramps and fullness in the epigastrium point toward the gall bladder

as the locus of infection. Again, gall-bladder disease is common in pernicious anemia. In addition one must pay attention to two other places as loci of infection — namely, the fracture site and the thrombophlebitis in the right leg. Inasmuch as femoral-vein ligation did not do much good, it seems that the infection was not localized in the veins of the leg.

There is additional evidence of liver disease — namely, failure to respond to vitamin K, a high serum protein (so common in the early stages of liver disease), reversal of the albumin-globulin ratio, a positive cephalin flocculation test and, finally, retention of bromsulfalein. Later on there is evidence that he was developing cardiac failure — namely, rales at the bases, an enlarging heart, diastolic gallop rhythm, a drop in blood pressure and edema of the ankles. Certainly he must have had some underlying arteriosclerotic heart disease that was made worse by the prolonged fever.

What about the diagnosis? I think we have to consider several diagnoses in this case. Since he had treatment I doubt that we can prove the presence of pernicious anemia, and I believe that the pathologist will also be unable to make this diagnosis. The patient undoubtedly had cirrhosis in the early stage which was made worse by infection or by drugs. He had sulfonamides twice, and in the presence of liver disease they can cause additional damage. It is possible that he never had pernicious anemia, because in cirrhosis there frequently exists a hyperchromic anemia that can be mistaken for pernicious anemia. Since this anemia also responds to liver, there is a way of distinguishing one from the other after treatment. Undoubtedly he had arteriosclerotic heart disease with congestive failure.

The important problem is to determine the cause of the prolonged fever. A patient with cirrhosis may have superimposed hepatitis, which can give a prolonged spiking fever. If this were the case, the patient would have had jaundice. Since there is mention of jaundice we can rule out hepatitis superimposed on cirrhosis.

Malignant disease in various locations might produce prolonged fever. Could this fracture have been a pathologic fracture? I can find no clue in the record that it was. Hepatoma, which sometimes supervenes in cirrhosis, can be the cause of fever. Carcinoma of the stomach should be mentioned since it is frequently associated with pernicious anemia. The patient certainly had not had carcinoma of the stomach for ten years. He could have had polyps of the stomach that had undergone malignant degeneration. There is, however, no evidence for this diagnosis; I merely mention it. Lymphoma should always be mentioned, particularly the type located in inaccessible regions, such as the retroperitoneal lymph nodes. Multiple myeloma is suggested by the high serum protein, but that is the only evidence we find for such a diagnosis.

Could there have been any sepsis coming from the wound itself? Although the statement is made that "there was no evidence of extending infection," there was, enough to produce thrombophlebitis. Other types of infection should be considered, such as generalized or miliary tuberculosis. I merely mention them, but find no evidence for them. The same is true for subacute or chronic endocarditis, and for certain types of noninfectious diseases, such as periarteritis nodosa and lupus erythematosus disseminata, any one of which may cause prolonged fever.

I should like to see the films of the lungs.

DR. LAURENCE L. ROBBINS: These films demonstrate the fracture, but I do not believe that we need to spend time on them. I do not see anything that suggests a pathologic fracture.

These two films of the chest were taken one month apart while the patient was in the hospital. This portable film was taken during the last acute episode. About the only thing I can see of significance is the diffuse increase in the markings throughout the lungs, which could have been on the basis of increase in size of the vascular or lymphatic channels. The ribs do not suggest myeloma. Terminally there are areas of density. I am not sure of their significance because the film was taken with a portable machine and there was motion; however, one would have to consider multiple small infarcts. From the abdominal film one can say that the spleen was certainly enlarged. There is an indefinite shadow of calcification overlying the left kidney, which is possibly outside the kidney. The bones of the lumbar spine and pelvis show no degenerative changes or evidence of multiple myeloma.

DR. LERMAN: There are two places where the evidence points to the presence of infection. One is the kidney pelvis, the substance of the kidney or the tissues around the kidney. Such an infection, with resulting thrombophlebitis, could have accounted for pulmonary emboli. The other locus of infection is the gall bladder. There were, however, no localizing signs in the region of the gall bladder. Another possibility is repeated emboli from the thrombosed femoral vein. Although this is unlikely because of the bilateral femoral-vein ligation, there is a possibility that the thrombus extended beyond the point of ligation, continued to throw off emboli and thus produced pulmonary infarcts. In any case the x-ray findings may be explained either by repeated pulmonary infarcts or by terminal bronchopneumonia. They certainly do not suggest metastases.

I shall have to conclude that this patient had an infection either in the kidney or in the gall bladder, or in both, but I do not know what type of infection.

DR. J. H. MEANS: I thought the chills were impressive. I wondered if he could have had a staphylococcal pyemia, with abscesses in the kidney, liver and elsewhere. The negative blood cultures do not rule out the diagnosis.

DR. FLETCHER H. COLBY: Where was the primary focus?

DR. MEANS: I do not know.

DR. JAMES B. AYER: You did not say anything about the Parkinsonian feature. Does it fit in?

DR. LERMAN: No, except for the fact that the patient was very sick.

CLINICAL DIAGNOSES

Pylonephritis.

Hepatitis.

Bronchopneumonia.

DR. LERMAN'S DIAGNOSES

Renal infection (? type)?

Cholecystitis?

Portal cirrhosis.

Arteriosclerotic heart disease.

Pulmonary infarction.

ANATOMICAL DIAGNOSES

Pulmonary tuberculosis.

Miliary tuberculosis of liver, spleen, kidney, and bone marrow.

Portal cirrhosis of liver.

Mycotic aneurysm of sinus of Valsalva (tuberculous).

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: This man was a puzzle on the surgical ward, and the surgeons called in the medical men frequently to see if they could find out the cause of the prolonged fever. The surgeons believed that the cause of the fever had nothing to do with the fracture.

At autopsy, we found both lungs expanded and almost completely solid. On section, numerous small cavities that looked like broken-down abscesses were seen. It was thought that the disease was a diffuse bronchopneumonia with secondary abscess formation. Another interesting finding was in the aorta. Just above the aortic valve there was a tear in the intima with the formation of an aneurysm into the sinus of Valsalva. The aneurysm measured 3 cm. in diameter and had not ruptured.

Microscopic examination of the lung showed that this man had an acute diffuse tuberculous process throughout the lungs — a tuberculous pneumonia. He also had miliary tuberculosis of the kidneys, liver and spleen. The aneurysm in the aorta proved to be a mycotic aneurysm due to tuberculosis, a very unusual occurrence. In addition to miliary tuberculosis, the liver showed evidence of an old portal cirrhosis. We were unable to find any evidence of pernicious anemia as Dr. Lerman predicted; there were large amounts of hemosiderin in the marrow spaces, as well as miliary tubercles, but no evidence of red-cell hyperplasia.

DR. COLBY: I was not here for the first part of this discussion, but it is interesting that, although the history states that the urine was negative, the patient had renal tuberculosis. In my experience in the past ten years I have never seen a case of renal tuberculosis that did not show albumin in the urine.

DR. CASTLEMAN: This was miliary tuberculosis, which I judge developed in the kidneys during the last two months of his stay. It was not a primary renal tuberculosis.

DR. LERMAN: Was there any evidence of recent hepatic disease?

DR. CASTLEMAN: No, with the exception of the tuberculosis.

CASE 30092

PRESENTATION OF CASE

A fifty-nine-year-old unemployed painter entered the hospital because of anorexia.

The patient had never been a "big eater." About five months before entry, however, he gradually lost his appetite so that he eventually ate "almost nothing." For a few weeks before entry his daily diet had consisted entirely of an éclair and one or two glasses of milk. Two months before admission he began to have a sensation of generalized abdominal pressure, which occurred two or three times daily, lasted one hour and was most severe in the morning. Two weeks prior to entry he began to have a strange, sharp precordial pain every two hours; this lasted five or ten minutes, and was relieved by eating and eructation and to a lesser degree by alkalies. He became progressively weaker, and for the week preceding entry had been so shaky that he fell when walking. He had been constipated for months, having had only two bowel movements weekly. The last bowel movement was one week before admission, at which time he thought that he recognized food eaten in the morning. He had had no abdominal pain, nausea, vomiting, hematemesis, melena, fever, chills or urinary symptoms. He had lost 40 pounds of weight since the onset of his illness.

Physical examination showed a pale, emaciated man who looked older than his stated age. Examination of the heart and lungs was negative. The abdomen was scaphoid. There were no masses, tenderness or spasm. The liver and spleen were not palpable. The lower poles of the kidneys were palpable. The cecum and sigmoid were felt and appeared normal. Rectal examination was negative.

The blood pressure was 135 systolic, 56 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a white-cell count of 19,100, with 76 per-cent neutrophils. The hemoglobin was 8 gm. The urine was negative. The stools were guaiac negative. The blood protein was 4.8 gm. per 100 cc. A blood Hinton test was negative.

A gastrointestinal series showed a normal esophagus. The fundus of the stomach was not well visualized. A small amount of barium appeared to pass backward into the fundus, but the upper portion seemed to be filled by a rather smoothly demarcated mass. Within the mass there was a peculiar round air shadow, but that portion could not be filled with barium. A localized bulge of the diaphragm was seen in the region of the mass. Study of this area, however, was difficult because of the patient's emphysema. The remainder of the stomach and the duodenal cap were not remarkable. In about two and a half hours barium was seen in the transverse colon.

A gastroscopy on the twelfth hospital day showed the mucosa of the body of the stomach to be somewhat pale but not definitely atrophic. Close to the cardiac orifice, and extending into it, was a rather smooth, rounded mass measuring 5 cm. in diameter; there was no evidence of ulceration.

The patient was given two transfusions of 500 cc of blood each, and an operation was performed on the thirteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD HAMLIN, JR.: I think it is fair to say that the abnormal laboratory findings were due to cachexia. The patient had eaten nothing but éclair for a long time, and there is no reason why he should not be anemic, and have a low blood protein as well. On the other hand, he may have had loss of blood. Since Dr. Benedict is here, I wonder if he could enlarge on the gastroscopic examination.

DR. EDWARD B. BENEDICT: I said that no ulceration was "visible." I could not see around the tumor. Furthermore, I said that there was a blood clot hanging from the lower margin of the tumor.

DR. HAMLIN: That is of considerable interest. I tried to imagine a gastric tumor without ulceration and with air in the center, and that led me to wonder whether a lipoma could show increased radiance that might be mistaken for air. Dr. Benedict's visualization of a hanging blood clot makes that extreme unlikely.

DR. LAURENCE L. ROBBINS: This spot film perhaps shows the lesion to the best advantage. Normally, we should expect to see the fundus of the stomach extending backward in this region. Here we find a relatively smooth mass that apparently fills the greater portion of the fundus. Incidentally, this is a place that is particularly difficult for a gastroscopist to see. The air shadow is present on several films, but at no time were we able to get any barium into it. The statement is made in the record that the examination of the area was difficult because of emphysema. That is simply because this area is beyond the reach of palpation, and to determine the changes we like to make use of the diaphragm. This patient had so much emphysema that the diaphragm

did not move well, and the examination was difficult, but I think that there was a tumor.

DR. HAMLIN: From an academic point of view is there increased radiance in lipoma of the stomach?

DR. ROBBINS: I have never seen one, but I think there should be if lipomatous tissue is surrounded by barium or by tissue with the density of water, such as mucous membrane, muscle and so forth.

DR. HAMLIN: I must try to determine what type of gastric tumor this was. It obviously does not seem to have been a typical carcinoma of the stomach because of its location and also because of its appear-

case, although we did not give much weight to either diagnosis because of the absence of any real evidence of bleeding except microscopically. In my experience many of the patients with leiomyosarcoma have had massive hemorrhage.

A transthoracic incision was made. As soon as the diaphragm was visualized it was obvious that we were dealing with a carcinoma that had invaded a large portion of the central tendon of the diaphragm. A free portion of the diaphragm near the costal margin was incised and the abdomen opened. A massive tumor arising in the stomach and invading the spleen and



FIGURE 1. Cross Section of the Tumor Mass, Showing Extension from the Stomach into the Spleen.

ance by x-ray and by gastroscopy. Was it malignant or was it one of the rare benign forms of tumor? Statistically, it is more likely to have been malignant. Furthermore, the fairly short history and the age of the patient suggest a malignant tumor.

I am not going to go through the various types of tumor that can be found in the stomach. Leiomyoma, fibromyoma and sarcoma are the most likely ones in that portion of the stomach under these circumstances. The fact that an air shadow was present indicates in all probability a small fistulous tract from the center of the tumor to the interior of the stomach and, as Dr. Allen has pointed out on occasions, that is almost pathognomonic of the leiomyosarcomatous type of lesion. I shall leave it at that.

DR. RICHARD H. SWEET: We considered lymphoma and leiomyosarcoma as possible diagnoses in this

the tail of the pancreas was found. At first it seemed almost impossible to remove this growth because of its invasion of diaphragm, spleen and pancreas, but it was finally decided that an attempt was worth while. As a result we completed the operation successfully, after having resected a large portion of the stomach with a piece of the diaphragm attached, the spleen, the left adrenal gland and about half the pancreas. Restoration of continuity was carried out by performing an esophagogastric anastomosis. The patient made a good recovery and has since left the hospital.

CLINICAL DIAGNOSIS

Carcinoma of stomach.

DR. HAMLIN'S DIAGNOSIS

Leiomyosarcoma of stomach.

ANATOMICAL DIAGNOSIS

Adenocarcinoma of stomach, with extension into spleen, pancreas and diaphragm.

PATHOLOGICAL DISCUSSION

DR. RONALD C. SNIFFEN: As Dr. Sweet has indicated, the description of this specimen is like a summary of the abdominal cavity in *Gray's Anatomy*. A 2-cm. segment of the esophagus was resected, a portion of the stomach and pancreas, the spleen, the left adrenal gland and a section of diaphragm.

The tumor lay high on the left wall of the stomach and was approximately 4 cm. in diameter, rather nodular; in its center there was a wide crater. This crater penetrated the tumor and led into the spleen (Fig. 1), which was adherent to the stomach and almost entirely replaced by tumor. In addition the neoplasm had invaded the pancreas, surrounded the adrenal gland and had invaded itself on the diaphragm.

Microscopically it was a Grade II adenocarcinoma that had arisen from the gastric mucosa.

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THE JOURNAL does not hold itself responsible for statements made by any contributor.

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COMPULSORY HEALTH INSURANCE

Two articles appearing elsewhere in this issue of the *Journal* deserve careful and thoughtful reading. In one, Mr. I. S. Falk, director of the Bureau of Research and Statistics, Social Security Board, clearly and simply outlines the principles and philosophies that have been responsible for the Wagner-Murray-Dingell Bill. In the other, Dr. Nathaniel W. Faxon, director of the Massachusetts General Hospital, discusses the pros and cons of compulsory health insurance, and makes an appeal for the utilization of existing agencies for the provision of medical care if compulsory insurance is judged to be necessary.

In spite of the remarkable advances of American medicine, there is no doubt that many people of this

country either lack facilities for medical care or receive poor medical care; on the other hand, the number is undoubtedly lower than that claimed by the groups that favor a radical change. The fact that, by and large, the mortality rates for specific diseases are as low in the United States as in any other country of the world is no guarantee that medical and hospital practice is perfect. As previously commented on editorially,¹ the health of the Nation is largely influenced by many nonmedical factors—decent wages, a high standard of living, unsurpassed educational facilities, excellent means of transportation and well-endowed and well-administered charitable organizations. To disregard these influences and to argue that medical and hospital practice is beyond criticism is plain stupidity, and one of the reasons why the attitude of many physicians and professional organizations toward the problems of medical care has received little sympathy from certain laymen and physicians who are more keenly aware of the actual state of affairs. On the other hand, there seems to be little excuse for radical experimentation, with the adoption of an entirely different scheme of medical and hospital practice. As aptly stated in *Hospital Progress*,² "Has the present system proved so inefficient, so hopelessly useless, so economically unsound, so professionally barren, as to make it necessary, if we must remedy the alleged shortcomings of our present system, to appeal to an incredibly different pattern of medical care?"

Every effort should be made to improve the health of the Nation, but the present system of medical and hospital care need not be discarded to accomplish this ideal. The process should be one of evolution, not one of dissolution. Organizations offering voluntary insurance have traveled far in the last five or ten years, and those under the control of physicians and hospital administrators assure a quality of service that can never be duplicated by a scheme in which bureaucracy and politics play essential roles. Certainly, the principles embodied in the letter sent to all congressmen from New England by their respective medical societies³ deserve careful consideration. If compulsory insurance ever becomes necessary, it should be at the state level, since conditions in different parts of the country are so vari-

ANATOMICAL DIAGNOSIS

Adenocarcinoma of stomach, with extension into spleen, pancreas and diaphragm.

PATHOLOGICAL DISCUSSION

DR. RONALD C. SNIFFEN: As Dr. Sweet has indicated, the description of this specimen is like a summary of the abdominal cavity in *Gray's Anatomy*. A 2-cm. segment of the esophagus was resected, a portion of the stomach and pancreas, the spleen, the left adrenal gland and a section of diaphragm.

The tumor lay high on the left wall of the stomach and was approximately 4 cm. in diameter and rather nodular; in its center there was a wide crater. This crater penetrated the tumor and led directly into the spleen (Fig. 1), which was adherent to the stomach and almost entirely replaced by tumor. In addition the neoplasm had invaded the pancreas, had surrounded the adrenal gland and had implanted itself on the diaphragm.

Microscopically it was a Grade II adenocarcinoma that had arisen from the gastric mucosa.

OBITUARY

ROY DENNIS HALLORAN

1894-1943

The death of Roy Dennis Halloran has taken from the neuropsychiatric section of the medical profession of this state and of the country an eminently capable man in the most productive period of his life. His death is a great loss for this state in particular, for he had contributed much in broadening the ideas on the hospital care and treatment of those who are mentally ill. No doubt were he to have lived and to have resumed his professional activities in Massachusetts, a great deal more could have been expected from him.

Dr. Halloran was born in Cambridge, Massachusetts, on August 4, 1894. He received his secondary education in the Boys' High School, Brooklyn, New York, and his A.B. degree *cum laude* from Dartmouth College in 1917. He received his M.D. degree from the College of Physicians and Surgeons, Columbia University, in 1920. After two years' internship in the Newark City Hospital he entered the field of psychiatry and became assistant physician and then senior physician at the Boston State Hospital. In 1928, he was appointed assistant superintendent of that hospital, where he combined clinical psychiatric work with research. Under guidance of Dr. James V. May, then superintendent of the Boston State Hospital, he developed into a capable clinical psychiatrist and an efficient administrator. From 1925 to 1933, he actively participated in research work carried at the Research Department of that hospital, under the guidance of Dr. Abraham Myerson, with whom he published several important papers. Their technic for obtaining blood from the internal jugular vein and internal carotid artery was a particularly outstanding contribution, for it offered a new method for the study of cerebral metabolism in nervous and mental diseases. This method became widely known and served as a basis of important contributions in this country and abroad. In 1929 he was appointed assistant to the Commissioner of Mental Diseases, and in 1933 became the first superintendent of the Metropolitan State Hospital, then in the process of construction and organization. During the nine years of his superintendentship he not only applied to this institution the high standards of psychiatric hospital administration for which our state has a long-standing and countrywide reputation, but with courage and energy broadened the functions of the state psychiatric hospital as a center of research and teaching in the care and treatment of the mentally ill. Thus, he designed and developed at the hospital the Medical and Surgical Centre of 400 beds as a complete general-hospital unit, which was approved by the American College of Surgeons in 1936. This was the first medical and surgical unit of a state psychiatric hospital to be approved in New England.

He developed a patients' library as a special department under a trained librarian, not merely as a diversional facility but as a part of the program of psychotherapy, the reading material being selected in accordance with the special psychologic requirements of each patient. He made special efforts to break the wall of psychologic and social isolation of the patients under prolonged treatment at the hospital. The theatricals and garden parties, and the exhibits of the patients' paintings, carvings and crafts held annually at the Metropolitan State Hospital, were favorably noted by the general press. He possessed outstanding abilities as a team builder and maintained high standards of morale and interest among the staff and employees of the hospital. In 1936, under the impetus of the establishment of the American Board of Neurology and Psychiatry for the certification of specialty, he organized post-graduate seminars in this branch of medicine. These have been held annually ever since and close to four hundred physicians—members of the staffs of psychiatric state hospitals and practitioners in Massachusetts and the adjoining New England states—have availed themselves of this educational opportunity. The seminars showed in a practical way how the teaching facilities of a state hospital can be effectively integrated with the teaching programs of university centers and medical schools to the advantage of large groups of physicians and students. Under his direction, the lectures of the seventh seminar, held during the fall and winter of 1941-1942, were transcribed and published in three volumes, each covering the lectures of one of the three semesters: "Military Neuropsychiatry," "General Psychiatry" and "General Neurology." The *Collected Lectures*, privately published at the Metropolitan State Hospital, have become widely known and are in great demand by young members of the profession, especially those who are in military service. He himself contributed much as a lecturer on administrative and clinical psychiatry at the seminars and as professor of clinical psychiatry at Tufts College Medical School.

In August, 1942, Dr. Halloran was called to take charge of the Neuropsychiatry Branch of the Office of the Surgeon General, being commissioned as a colonel in the Army of the United States. He accepted this call as a matter of duty to his country but hoped to return to the Metropolitan State Hospital after the war and to continue the work that he loved so much. While in Washington, he performed the difficult task of organizing the neuropsychiatric service of the Army during mobilization on an unprecedented scale. To his duties in military service, as usual, he gave all of himself. He died of a coronary occlusion on November 10, 1943, and was buried in the Arlington National Cemetery.

Dr. Halloran was a member of the American Medical Association, a fellow of the American Psychiatric Association and a member of the Amer-

ican Hospital Association. He was president of the New England Society of Psychiatry in 1940-1941, and president of the Massachusetts Occupational Therapy Association for two terms, 1939-1940 and 1940-1941. In 1938, he was representative from New England at the Conference on Behavior Problems of School Children in Washington, D. C. In 1939, he was a delegate of the Department of Mental Health at the American Psychiatric Convention. In 1940, he was member of a civil-service panel for the selection of a hospital superintendent in Rhode Island. He was a member of the Dartmouth Alumni Association and the University Club of Boston, as well as president of the Belmont Rotary Club in 1940-1941. He belonged to Sigma Phi Epsilon, Alpha Kappa and Gamma Alpha fraternities.

P. I. Y.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BARRY — Thomas A. Barry, M.D., formerly of Boston, died August 4, 1943, in the service of his country. He was in his thirty-fifth year.

Dr. Barry received his degree from Tufts College Medical School in 1936. He was a member of the Massachusetts Medical Society and the American Medical Association.

His mother survives.

CLARKE — Willis E. Clarke, M.D., of West Somerville, died February 23. He was in his fifty-seventh year.

Dr. Clarke received his degree from Tufts College Medical School in 1912. He was on the staff of the Cambridge City Hospital and Tufts College Medical School and was a lecturer for many years at the Boston Dispensary. Dr. Clarke specialized in diseases of the ear, nose and throat. He was a member of the Massachusetts Medical Society and the American Medical Association.

Two brothers and a sister survive.

SPELLISSY — Frank T. Spellissy, M.D., of Marlborough, died February 4. He was in his forty-ninth year.

Dr. Spellissy received his degree from Tufts College Medical School in 1919. He was a member of the staff of the Marlborough Hospital and a member of the Massachusetts Medical Society and the American Medical Association.

Two brothers survive.

WAR ACTIVITIES

INDUSTRIAL HYGIENE

"FUMES FELL 38 WORKERS"

Such were the headlines in all the Boston papers on December 11, 1943, when, according to the newspaper accounts, 38 women employed at a Cambridge plant had fallen unconscious from a mysterious gas.

Investigation by members of the staff of the Massachusetts Division of Occupational Hygiene revealed that the "mysterious gas" was carbon monoxide and that, of the 38 workers affected, only 8 required hospitalization for a single night. There were no fatalities or apparent sequelae. Atmospheric contamination with carbon monoxide occurred from the use of two brazing furnaces and a combustion chamber in which illuminating gas was reduced to a mixture of carbon dioxide 8 per cent, carbon monoxide 12 per cent, and nitrogen 80 per cent. A leak was found around the sight glass of the combustion chamber, but the primary cause of the poisonings was the breakdown of a ventilating fan.

The plant was immediately shut down, and the furnaces were run experimentally at night. Within one hour, concen-

trations in excess of 100 p.p.m. were found with a temporary 16-inch fan in operation; twenty minutes after the fan was stopped, concentrations in the workroom reached 280 p.p.m. Steps instituted to prevent a recurrence included more adequate exhaust ventilation, a carbon monoxide alarm and segregation of the furnaces from the main workroom.

The moral of this story would seem to be that a situation involving an extremely "close call" for a sizable group of workers might at any time be duplicated in many plants in Massachusetts and other states, and that operations such as the one in question call for more attention than they have been getting. — Reprinted from *Industrial Hygiene News Letter* (January, 1944).

MISCELLANY

NOTES

On February 28, Dr. Richard P. Strong, formerly professor of tropical medicine at Harvard Medical School and at present director of tropical medicine at the Army Medical School, Washington, D. C., was awarded a medal and an honorarium by the American Foundation for Tropical Medicine in recognition of his distinguished service in tropical medicine. The awards were made possible by a recent gift to the Foundation from the Winthrop Chemical Company, and will subsequently be given periodically for outstanding contributions in the field of tropical medicine, the medal to be known as the Richard Pearson Strong Medal.

The Trustees of Boston University have announced that Dr. Charles F. Branch, professor of pathology, has been appointed dean of Boston University School of Medicine. He will assume his new duties immediately, and succeeds Dr. Bennett F. Avery, who recently resigned to become director general of public health in Iran. Dr. Branch has held a teaching position in the medical school for the past eighteen years and has been professor of pathology since 1932.

CORRESPONDENCE

SIGNED VERSUS UNSIGNED BOOK REVIEWS

To the Editor: For many years I have had an interest in book reviews in medical journals. As a younger man not infrequently I wrote book reviews for the predecessor of the *Journal of the Boston Medical and Surgical Association*; in later years I have been at the other end of the book-review problem, reading reviews of my own publications. In each capacity I have thought that signed reviews were preferable to anonymous ones.

A book review can be a real contribution to medical literature in its style and content; not infrequently this actually happens with reviews in the field of general literature. But natural that, if one carefully reads a book and then fairly and comprehensively discusses its contents, he will like to credit for his work by his identity's being known. To read that the medical reading world is going to see who wrote a review seems to me calculated to stimulate a reviewer to make a greater effort to produce something that will be a credit to the writer and to check any tendency to careless reviewing. It is my belief that a plan of having signed reviews will bring to the work more capable reviewers. As a reviewer I should have preferred to have my name appear.

As an author my experience has been that reviews are very helpful toward better subsequent editions, and that this is one of the important usefulnesses of a book review, the other being to indicate to the reading public the content of the book and its quality as a guide to the desirability of its purchase. With reviewers, including critical ones, I have often had both delightful and extremely helpful correspondence. So I like to know to whom to write. Journals that publish unsigned editorials often say they will forward your letter to the reviewer and so allow you to have the advantage that might come from correspondence with the reviewer. I have tried this; either my letter remained unanswered, or the answer from the anonymous reviewer somehow did not seem to be the satisfactory results that came from correspondence with

a known reviewer, with whom you talked by letter as man to man.

Usually it is said that the anonymous reviewer is freer to criticize. That may be true, but it has not been my experience, for, by and large, signed reviews of my books have been just as critical as the anonymous ones, possibly even more so. My reviewers have not appeared to be afraid to be critical, and their criticisms have helped me, particularly when, by correspondence, I obtained elaboration of the criticism toward a better understanding of it on my part and in addition, what has been very helpful, numerous criticisms that had not been included in the published review. For the author I think signed reviews are a greater help than the unsigned.

I take it that the chief object of a book review is to be a help in the selection of books to purchase. Certainly, if the reader is aware of whose opinion he has seen, that opinion will carry increasing weight in proportion to the position in the medical world held by the writer of the review. It is my belief that in general a higher-grade medical man can be obtained to write signed reviews and that this type of man is entirely willing to say what he thinks of a book and less apt to be fulsomely uncritical of a book deserving condemnation rather than praise.

It seems to me that the policy long practiced by the *Journal* is not conducive to obtaining reviews of so high a grade of excellence or so helpful to readers and authors as would come from having signed reviews. Anyhow, why not try the other way for a while to see whether or not it is a better way rather than, without trial of the other way, persist in the present practice? If it does not seem preferable after a few months of trial, then return can be made to anonymity.

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To the Editor: I am sure your readers are glad that the secretary of the Society has made public in your columns "the exact policy adopted by the Council on Medical Education and Hospitals of the . . . with regard to students from . . . being accepted by approved h . . ."

They may perhaps be interested in a statement which makes clearer than anything I have seen published some of the conditions under which this policy was formulated.

In June, 1942, I requested permission of the Council on Medical Education and Hospitals to make representation in person to it, concerning the question of penalizing action by the Council, in the case of a hospital approved by it if such hospital accepted as clinical clerks students from a school not approved by the Council. I had been told by a number of hospitals that they could not accept Middlesex students because the American Medical Association would not approve, but I had found by the spring of 1942 no authoritative written or printed statement supporting the contention of the hospitals.

Permission was granted to me and at the meeting in Atlantic City I told the Council briefly what I had been doing in Massachusetts about substandard medical education and especially what I had undertaken to do at Middlesex, and I asked the question to which I have referred, namely, "Will the Council withdraw approval of a hospital approved by it for the training of interns if such hospital accepts as clinical clerks the students from a school not approved by the Council?"

The letter from the Council, dated June 7, 1942, did not answer my question but contains the following sentence, "The Council did not feel justified in offering any approval or even encouragement in connection with your efforts, but we will await with interest any further report."

I laid the matter before the president (or maybe it was the president-elect) of the American Medical Association. He said in substance, "At least you are entitled to an answer to your question." So I wrote again, referring to what I called a "misunderstanding." The reply, dated June 19, 1942, reads in part as follows:

I am sorry if any misunderstanding has resulted from my letter of June 7. In connection with the approval of hospitals for internships, the hospitals deal individually

with the Council on Medical Education and Hospitals. As you fully realize, conditions vary greatly in the different hospitals and many of them are approved or removed from the list temporarily because of certain conditions existing at a specific time. The interest of the Council in this connection is solely the maintenance of a satisfactory educational program for the training of interns.

Hence if a hospital maintains such satisfactory standards the Council would not consider it within its field to decide whether or not it should accept students from any medical school as clinical clerks. . . .

Because of the possibilities of misunderstanding and because of the varying conditions existing in hospitals approved for internships, together with the responsibilities of the Council in the field of undergraduate medical education, the Council did not feel justified in making any general overall statement.

In spite of this disclaimer on the part of the Council, that answer sounds like a statement of policy. But it seems to have been in some respects not the right answer as is shown by the statement of the "exact policy of the Council" published in the January 20 issue of the *Journal*. I have been informed by the secretary of the Council that this policy was adopted on November 7, 1943.

It is the paragraph which I have quoted from the letter of June 7, 1942, which is most significant as indicating the background of the discussion. It is so important that I quote it again, "The Council did not feel justified in offering any approval or even encouragement in connection with your efforts."

What are my efforts? For eleven years as secretary of the Board of Registration in Medicine my efforts had been

School of Medicine to continue my efforts by attempting to improve that particular school.

It is not necessary to explain why I had not asked the approval or encouragement by the Council for my efforts except to point out that my own conscience was clear, to me a deciding factor.

If the justification for the existence of the Council is *their* effort to improve medical education, why their disclaimer as to "approval or even encouragement"? The principles on which my proposed action was to be based are highly orthodox, although I hope that some novel practices may be introduced in the course of time. Why, then, could no approval or even encouragement of efforts be offered?

But there the record stands. "The Council did not feel justified in . . . connection with . . . education. F . . . illuminating . . . one to think furiously."

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BOOK REVIEWS

The Compleat Pediatrician: Practical, diagnostic, therapeutic and preventive pediatrics. By Willburt C. Davidson, D.Sc., M.D. Fourth edition. 8°, cloth, 256 pp. Durham, N. C.: Printed by Seeman Printery for Duke University Press, 1943. \$3.75 by check with order, or \$4.00 on credit.

This fourth edition differs little from previous editions, having been merely brought up to date so far as is possible with rapidly advancing medical information.

One's first impression on examining a book of this sort is one of bewilderment and helplessness. When, however, one has mastered the method of searching for information, the original emotion changes to one akin to awe that so much valuable, utilizable, up-to-date information is so readily available in such a small volume. In particular, there are many accurate and valuable tables, which not only include growth and diagnosis . . . each group . . . practicing physician.

In the reviewer's opinion the chief worth of this remarkable volume lies in its value as a book of reference to the student

and intern and to the general practitioner who may be confronted with pediatric problems.

Burns, Shock, Wound Healing and Vascular Injuries. Prepared under the auspices of the Committee on Surgery, Division of Medical Sciences, National Research Council. *Military Surgical Manual V.* 8°, cloth, 272 pp., with 20 illustrations. Philadelphia and London: W. B. Saunders Company, 1943. \$2.50.

The present war has brought into the armed services certain doctors who are ill equipped to deal with wounds and their many complications. The spread of specialization has made it impossible to recruit the large number of men who are needed and at the same time qualified to deal with war wounds. In the interest of efficiency, standardization of front-line and base-hospital practice is essential. The two-fold purpose of instructing the less experienced and of unifying practice among various units is well served by the military surgical manuals published by the National Research Council.

The volume on burns, shock, wound healing and vascular injuries is compiled by experts. It is thorough, concise and intensely practical. The keynote of the articles is proper treatment given early. Thus in severe burns the use of skin grafting is begun early; in shock, replacement therapy commences with the suspicion of shock; and in wounds, débridement is used within a few hours after injury.

Some of the problems discussed have not received their final solutions. The surface treatment of burns remains in a chaotic state. After outlining many measures of treatment the authors state:

It would be simple if one could be dogmatic and advise the use of one method, for example application of tannic acid, in treatment of all burns. However, it is now evident that it is unwise to try to apply any one method to burns of all degrees in all anatomic situations. Many other factors enter into the choice of local treatment. These include the availability of materials, time and space for certain of the methods, duration of time injury and so on. . . . Further experience may change the indications but possibly not the details of procedure of these methods.

The chapters on shock and fluid replacement are necessary for the war surgeon but contain much the same material as any recent volume on surgery. The chapter on skin grafting for contractures following burns is itself worth the price of the book. It is brief and yet has such a wealth of detail that one not widely experienced in plastic surgery can easily follow the procedures described. It will be of great interest to anyone doing general or plastic surgery.

Allergy. By Erich Urbach, M.D. With the collaboration of Philip M. Gottlieb, M.D. 4°, cloth, 1073 pp., with 395 illustrations and 59 tables. New York: Grune and Stratton, 1943. \$12.00.

This book covers the subject of allergy from almost every viewpoint and is really an encyclopedia on the subject rather than a textbook. The author presents in considerable detail the story of allergy from its genesis to the present and covers it in a most interesting and readable manner. The author in the preface states that he has attempted to give an impartial presentation of the conflicting views on controversial questions. He has succeeded admirably and presents his facts concisely and clearly.

The book is primarily one for the allergist, although certain chapters will have considerable interest for the general practitioner and specialists in other fields. Chapter 2, dealing with the basic principles of allergy, clarifies many of the difficulties of those unacquainted with the theories of this condition. This chapter and Chapter 19, devoted to the allergic diseases of the upper respiratory tract, should be valuable reading for most practitioners of medicine. One of the most interesting chapters is Chapter 23, which deals with allergic skin diseases, conditions that surely confront every physician, whether he is a general practitioner or specialist, sometime during his career. The facts in this chapter are presented with clearness, and the illustrations add considerably to the value of the text. In itself it constitutes a textbook that may well be read with profit by anyone seeking knowledge on the complex problems of allergic skin diseases.

Taken as a whole, although a bit unwieldy in size and voluminous in text, the book is a valuable contribution to the study of allergy and to the practice of this specialty. It certainly will be a desirable addition to the library of every practicing allergist and will earn a place for itself as a reference book in the library of the general practitioner.

Body Poise. By Walter Truslow, M.D. 8°, cloth, 312 p. with 96 illustrations. Baltimore: The Williams and Wilkins Company, 1943. \$4.50.

The writer has produced a useful treatise on physical education. The anatomy and kinesiology involved in maintaining good poise of the body is described in detail. There are helpful chapters on static disabilities of the feet, on the recording of a treatment of faulty posture and on lateral curvature of the spine. Various sports are analyzed in relation to posture. This book concludes with a glossary of anatomical terms and those unfamiliar with the nomenclature. This book should be of value to the physical educator and to the physiotherapist.

A Manual of Clinical Therapeutics: A guide for students and practitioners. By Windsor C. Cutting, M.D. 12°, cloth, 609 pp. Philadelphia and London: W. B. Saunders Company, 1943. \$4.00.

This is a compact, complete manual on treatment easily applicable to the care of disease in its wide range. It is well set up, and is based on the clinical and teaching experience of the author at Stanford, London and Johns Hopkins. It can be highly recommended as a textbook on clinical therapeutics.

Essentials of Syphilology. By Rudolph H. Kampmeier, M.D. With chapters by Alvin E. Keller, M.D., and J. Cyril Peterson, M.D. 8°, cloth, 518 pp., with 87 illustrations and 15 tables. Philadelphia: J. B. Lippincott Company, 1943. \$4.00.

This text presents all that its author claims. It is an excellent presentation of the concept of syphilis as a systemic disease. It stresses the value of complete history-taking, thorough physical examination, and emphasizes what syphilologists have learned by experience — namely, that clinical diagnosis must be supported by darkfield or serologic evidence of syphilis.

The reviewer believes that careful study of the clinical manifestations in the early stages of syphilis needs more consideration than the author stresses, because the future of the patient depends on the ability to recognize these lesions so that they will not be mistaken for those of late syphilis. The reviewer also believes that a diagnosis of syphilis can be made on two positive serologic tests alone. Furthermore, older syphilologists will not agree with the author's opinion in certain controversial questions — for example, the treatment of patients with a history of twenty years' duration who have no clinical signs.

There are other minor points to which the syphilologist might take exception; the book is written, however, for the student and the general practitioner, and the reviewer recommends it as a practical, comprehensive guide for diagnosis and proper treatment. The discussions of the medical aspects, prevention and control of syphilis are carefully presented, and the suggested methods of therapy are authoritative. The book is easily read, well printed and abundantly illustrated, and will make a useful addition to the library of the student, general practitioner or specialist.

Whooping Cough. By Joseph H. Lapin, M.D. 8°, cloth, 112 pp., with 25 tables. Springfield, Illinois: Charles C Thomas, 1943. \$4.50.

The author brings into this book his own wide experience in the prevention and care of whooping cough, as well as an extensive review of the literature. The chapters on bacteriology, pathology and immunity reflect his intimate knowledge of the subject. The chapters on the prophylaxis of exposed children and of contacts are sound expositions of a highly debatable matter. Here, as in the chapter on treatment, he keeps his feet well on the ground and points out what is based on pure speculation and what is of proved value. Furthermore, he gives facts and figures to show the relative value of different methods of dealing with this extremely variable disease. The only criticism one can make is that the author seems to have hurried over the chapters on complications and on public health recommendations. It is hoped that in subsequent editions these chapters will be brought up to the high level of the rest of the work. The book should be invaluable to every pediatrician and to every physician and to all practitioners who are confronted with the problem of whooping cough.

(Notices on page x)

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THE PSYCHONEUROSES OF WAR*

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WE are here reporting findings obtained from a study of the first 200 neuropsychiatric cases admitted to a hospital of the United States armed forces somewhere in the South Pacific. This paper presents a statistical survey of the main findings, with a brief interpretation.

The importance of the problem of psychoneurosis in war is reflected in the fact that the number of neuropsychiatric cases rose from 12 to 17 per cent of total admissions during the first four months the hospital was in operation. Furthermore, an additional 6 per cent of cases were transferred to the Neuropsychiatric Service within the hospital as the result of consultations that revealed concurrent neuropsychiatric disorders. Thus, the neuropsychiatric cases among the total admissions amounted to 23 per cent, or approximately 1 case out of 5.

The distribution of these neuropsychiatric cases according to diagnosis is as follows: anxiety neurosis, 49 per cent; hysteria, 20 per cent; constitutional psychopathic state, 7 per cent; schizophrenia, 6 per cent; manic-depressive psychosis, 5 per cent; epilepsy, 4 per cent; and miscellaneous disorders, 9 per cent.

The term "war neurosis" is not used here since we have come to believe that a clearer picture of the neurotic reaction is obtained from the standard classification. In most of these cases it appeared that the hysterical mechanism was essentially a means of immobilizing anxiety by converting it into a symptom that resulted in relative freedom from anxiety at the expense of loss of physical or mental function. This process was seldom complete, so that an admixture of anxiety and hysteria was often found in the same patient. In arriving at a diagnosis hysterical reactions were emphasized because they appeared to be of more serious import than others and affected the prognosis accordingly. It is interesting to note that the percentage of cases

with anxiety neurosis was originally higher and continued so until recently, when a group of 70 patients arrived. Half of these were Army patients and over half of them were found to have hysteria, many of them giving a history of severe amnesia, which in some cases persisted on admission.

In attempting to analyze predisposing conditions, the most important factor was found to be a disturbance in the family background. This was strikingly constant in almost every case. Those patients who came from homes that were broken by separation, divorce or death, or distorted by neurotic parents, were found to have personalities insufficiently developed to deal rapidly or adequately with the problems of life, particularly with the problems of war. On the basis of the histories given by the patients — which in most cases have been accepted as reasonably reliable — we have attempted roughly to estimate this disturbance in the home environment as follows: normal, 4 per cent; slightly disturbed, 25 per cent; moderately disturbed, 42 per cent; and severely disturbed, 29 per cent.

These patients were all young men; 70 per cent were between the ages of seventeen and twenty-five. Six per cent had entered college. One third of the entire group had completed high school. Fifteen per cent had completed the eighth grade only, whereas 8 per cent had not gone that far. Their educational accomplishments were not considered remarkable or directly related to the type of psychoneurotic reactions that later developed.

One striking feature was that 30 per cent of the entire group gave a positive history of head injury associated with unconsciousness lasting fifteen minutes or longer, prior to entering the service. In most cases, however, this episode bore no obvious etiologic relation to the later developed psychoneurosis. But it is assumed that this previous head injury, in certain cases, may have been a contributing factor, by lowering the patient's resistance or adaptive capacity, or possibly by making him more susceptible to fatigue and impairing his repressive powers.

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Thirty-five per cent of the patients had previously experienced a psychic trauma of a sudden and overwhelming nature comparable to that of the combat situation. The commonest form of this traumatic experience was an automobile accident. The usual reaction was that of being shaky or jittery for a short time and being afraid of riding in an automobile or driving one for a longer time. Of those who had seen combat, 85 per cent had been suddenly upset by exploding bombs or heavy shelling near them. Some had been rendered unconscious and some had become acutely hysterical. It was difficult to determine the reactions accurately from the records available and from the patients' accounts, but the following is a fairly accurate résumé of what happened: unconscious, 50 per cent; dazed, 22 per cent; "went to pieces," 10 per cent; "bounced" (not unconscious), 8 per cent; amnesia for the event, 5 per cent; blindness (hysterical), 3 per cent; and "frozen," 2 per cent. Many of those rendered unconscious or dazed also had amnesia after recovering consciousness. Likewise, many of them became hysterical or "went to pieces" on regaining consciousness. Usually these reactions recurred during subsequent air raids and shellings.

The factors of fatigue and of intensity and frequency of repetition of traumatic stimuli are indicated by the number of weeks the patients were able to carry on in the combat zone before the development of a manifest psychoneurosis. Thirty-five per cent broke down in the second and third weeks, 10 per cent in the fourth week, and 35 per cent in the tenth, eleventh and twelfth weeks. No psychoneurosis occurred in the sixteenth to nineteenth weeks, and only 1 patient became ill in the twentieth week. Eight per cent of the acute disturbances occurred as the result of action at sea. These figures are correlated in part with the strain of combat action, in part with fatigue, and in part with constitutional inability to withstand and recover from traumatic stimuli. It is our impression that of these factors the constitutional predisposition or the neurotic makeup of the patient is the most important

organic brain damage that complicated the psychoneurotic reaction and unfavorably influenced the prognosis. This occurred in 12 per cent of those who had been subjected to bomb or shell blast. Another complicating factor was a schizoid personality without psychosis. This occurred in 10 per cent of the cases evacuated from the battle area. In about half these the diagnosis of prepsychotic personality would have been more accurate.

It was noted that many of the patients when on liberty, particularly their first one after return from combat, imbibed alcohol too freely. When questioned about this, their reply was that they used it "to forget." This correlated with the anxiety symptoms and with the psychic distress associated with them. The patients with hysteria, being relatively comfortable, drank less. Those with anxiety symptoms for the most part did not persist in their drinking because they quickly learned that the relief they obtained did not last very long. Alcoholism *per se* occasionally occurred as a symptom but was in no way a definite or a major problem, although alcoholic beverages were available. On the whole, the part alcohol seemed to play in the picture was a beneficial one. It was generally used as a relaxing agent for purposes of recreation, — usually in a social setting, — and to relieve or ameliorate the tension and the frustrations of war. Occasional moderate drinking when off duty or on leave is a part of the pattern of military life.

Loss of weight in the battle area was tabulated as an indication of the effect of the stress of battle conditions, and was also considered to be a fair measure of the physical-fatigue factor. The weight loss averaged twenty-two pounds over a period of one to twenty weeks. There is considerable approximation in this figure, but it is reasonably accurate (as one of our patients remarked, "There were no scales on the island"). In the early weeks after occupation, the rations of many of the combatants were considerably substandard — rice and cocoanuts, and of these only enough for one or two meals a day.

bat zone. This finding correlated over 95 per cent with anxiety symptoms. Enuresis in childhood had occurred in 15 per cent, but few had developed this symptom as the result of combat. There was no special relation of bedwetting to the particular psychoneurosis that the patient later developed. Walking and talking during sleep had occurred in 20 per cent of the cases and persisted in a few up to the time of admission. This was limited to those who developed hysteria.

Nightmares occurred almost universally among these patients, even after they had been evacuated to a place of safety, and they were severe enough to wake them. The patients reported that in their dreams they were terrified and often felt paralyzed — "I couldn't move" — "I couldn't run" — "I couldn't shoot my gun." Their psychic disturbance was so severe that the usual protective dream mechanisms failed to operate. The anxiety broke through, and not only woke the patient but also flowed over into the sympathetic nervous system and produced sweating and shaking comparable to the nocturnal terror reactions occasionally observed in disturbed children. Some patients vomited after their nightmares and attacks of nocturnal terror. Repetitive dreams of combat were absent only in the psychotic patients and in a few of the markedly hysterical patients who could not remember what they had dreamed. There was a tendency among the patients to talk about their dreams and relate them to each other, apparently on a cathartic — and slightly competitive — basis. At any rate, they appeared to get some relief from this sharing of anxiety. It appeared to be a sort of group autotherapy, which in most cases was more effective than were the attempts made by a few patients to repress their anxiety altogether. Most of the patients showed a tendency to talk about their combat experiences, which at times approached a compulsion. This was encouraged as a form of group therapy.

The recounting of dreams and the reiteration of combat experiences were interpreted as an attempt on the part of the patient — pushed by an inner drive, or unseen necessity — to relive and master or to be successful in a situation that had previously mastered him. It was as if the patient was utilizing the dream and the retelling of his experience in a new and relatively safe situation to desensitize himself from a strongly emotional conditioning that had originally and recently occurred in the face of actual danger. Since there were few opportunities for intensive individual psychotherapy, all group efforts of this type were encouraged and were utilized to the utmost. These efforts, however, were seldom entirely successful in the short time the patients were able to remain in the hospital, but they were not without certain benefits. In some cases, just as the dreams woke the patients, so did certain patients have to leave the group of patients who were

retelling their combat experiences or leave motion pictures that showed bombing and shelling. In such cases it was obvious that the anxiety accumulated faster than the patient could cope with it. An example of this occurred when "Mrs. Miniver" was shown near the hospital. Most of the neuropsychiatric patients had to leave when the "blitz" in the picture began, and most of them required extra sedation that night. On the whole they seemed better able to adjust themselves to noisy radio programs or excited newscasts received acoustically than they did to the visual stimulation by motion pictures. A possible reason for this was the fact that they had the power to turn the radio off if it became too disturbing, whereas with a motion picture they had to leave, thus absenting themselves bodily and again excluding themselves from the group that was remaining and even enjoying it. Many interesting and subtle individual and group reactions along these lines were observed.

As compared to bombs and shells, rifle and machine-gun fire seldom precipitated a neurosis. One reason for this was summed up in a statement so often made by the patients, "You can't fight a bomb." Many of the patients seemed to recognize that activity, action and motion in a tense and dangerous situation are of great therapeutic and stabilizing value in draining off the excitation as rapidly as it is produced. Many of them were in situations where they could not do this. Most of them were forced to lie in foxholes or hidden in brush or crouched behind trees for hours and had to take extremely heavy bombing or artillery fire. At night they had to remain motionless for hours close to the enemy, often under mortar fire.

It must be remembered that here we saw only those who were able to control their impulse to run or those who were held and prevented from doing so by others, as was often the case. Several of the patients told of seeing others who ran from covered positions, only to be blown to bits. Often they added, "I'm afraid I might do that if I went back." From these and similar observations and from the details of breakdowns reported by these patients it is apparent that if action or adequate emotional release does not occur, the pressure of the accumulated excitation breaks through the personality, fracturing it, — by short-circuiting the cortex, — and discharges into the nervous and muscular systems, resulting in primitive instinctual patterns of behavior. Such actions are inappropriate and may be fatal. This excitation also discharges into the autonomic nervous system, as indicated by rapid heart action, rapid breathing, sweating, frequent urination and occasional vomiting, which were interpreted as abnormal only when they recurred outside the traumatic situation. There was also frequent defecation, but the prevalence of dysentery made this hard to evaluate as a symptom. This disruption of the personality was recognized by the

patients, as indicated in their spontaneous statements: "I'm not the same any more" — "Nothing interests me since I was bomb-busted" — "Things aren't the same." They were unsure, shaken, emotionally defeated and ready momentarily to retreat. They had lost self-mastery and self-confidence and had found themselves at the mercy of hostile and overwhelming forces — both external and internal. They may be again overwhelmed. It is this situation that creates anxiety, which *per se* calls up further excitation. Thus the vicious cycle of this psychoneurosis becomes established. Any sudden sound will call up additional excitation, which, if strong enough, will push through the personality in the places already ruptured and result in primitive protective movements or in the diffuse expressions of fear and impotence, such as crying, shaking or heedless muscular movements, that are so commonly observed.

Previous mention has been made of the frequency with which these patients came from broken or distorted homes, and we re-emphasize the opinion that this is the most important of all the predisposing factors that have been analyzed.

In studying the home background a certain pattern became apparent. The mother was found to stand out. She was usually a "nervous" woman and had often had a nervous breakdown but was rarely hospitalized for it. She was easily excitable and quickly "went to pieces" under stress. She tended to worry, particularly about her children, and to be overly concerned about them. For example, most of the mothers had waited up for their boys to come in at night up to the time that they entered the service. The father seemed to be in the background. He was away at work much of the time, and when he was at home it appeared that he was not much interested in or affectionate toward the children. About half the fathers drank to excess. From these observations the following interpretation is made: The mother is an immature person who feels herself insecure and in her marriage tends to establish a childish dependent relation to her husband. This, somehow, is not successful; the reason is not clear. It may be that the husband is also trying to establish a similar relation, as indicated by the frequency of alcoholism. The mother accordingly makes many compromises but remains insecure and identifies herself strongly with her children. Along with her insecurity she also vaguely senses that the world is hostile. Her subconscious thinking may then run along these lines: "If the world is bigger than I am, it may overwhelm me; it is hostile. I shall therefore feel hostile toward it"; or, "If the world is hostile, then I can make no attachment to it, therefore I shall make a doubly strong attachment to my children." So it may be that she and her children come to form a unit and feel together, relatively helpless in a hostile world. They are unable to do anything about this except to suffer and to repress their

natural counterhostility. The chief result of this is that the mother and the child never learn to deal with hostility, particularly the child, who later becomes a patient.

As previously mentioned, the father was in the background most of the time. When he was drinking, however, there frequently occurred an explosion of verbal and often physical abuse, to which the mother usually reacted by an attitude of hopelessness and defeat, with fearfulness and anxiety in the intervals. In this way the acceptance of the overwhelming nature of hostility may have become established in the patient along with the necessity to avoid it.

In studying the relations between the patient and his mother, these points come out again and again, and are corroborated by the letters the mother sometimes writes to her son who is in combat. Often her letters are anxiety laden and disturb him accordingly. Without denying the possibility that this is a natural reaction on the part of any mother whose son has gone forth to battle and may be killed, it is a fact, vouchsafed by many, that when he went into combat he was more worried about the situation at home — as it had been relayed to him by his mother — than he was about himself. One patient stated flatly:

I wasn't worrying about myself so much as I was worrying about my mother and how she would feel if anything happened to me. I knew that she would be worrying if she knew, or she would be worrying anyway, so I guess I worried. She always worried a lot about me and about everything else. She was the worrying kind and that made me that way. She had a nervous breakdown when I left home and wrote and told me all about it. She made me feel that it was my fault. That was what was on my mind when we attacked, so I couldn't do much good.

This is a typical verbatim statement. It was repeated many times by soldiers, sailors and marines.

This vicious emotional cycle in the family setup was repeatedly described, and in nearly every case a mutually dependent neurotic relation existed between mother and child. The mother, in view of this emotional need, unconsciously tended to perpetuate this relation and thus attempted to prevent the son's growing up, since in so doing he would outgrow his need for her. Such a loss seems to be as great as though she had lost a part of herself. It is this child-to-child relation that she understands best and that holds the least danger from her point of view. The child's growing up and breaking away thus becomes a hostile act. But the mother cannot express her counterhostility, for this would more surely lead to the loss of what she is trying to hold. This situation leaves little room for either hostility or love, the latter of which on the mother's part would move her in the direction of aiding the child to develop into an independent adult. This inhibited emotional energy seems to find a common outlet in worry and concern. In the light of this situation the child remains immature, insecure and dependent and re-

flects the mother's shortcomings. He does not acquire security within himself. He can attain adulthood only by breaking his mother's hold (rebellion). Attempts in this direction produce such pain and suffering on the mother's part and lead to situations where he feels such insecurity and anxiety that he comes into the service with the fundamentals of this interdependent relation still essentially unchanged, not having dealt with his stronger forces — having lived a life chiefly receptive and more identified with his mother than with his father. Thus, it would appear that in the combat situation, being oriented toward life in a receptive way, he is more concerned with what is coming at him from the enemy than with what he is sending toward the enemy. The conscious complaints and the dreams of these patients were universally passive and receptive — "bombs falling on me" — "being chased by a shell" — "... shooting at me" — "... running at me with knives." Rarely was the patient shooting at the enemy, and then the story was usually, "I pulled the trigger but my gun wouldn't go off" or, "I tried to attack them but my arms wouldn't move" and so forth. In this respect it may be mentioned that a great many patients spoke of interesting relations between killing and sexual excitement that they experienced. There were also many psychosomatic relations, particularly those shown by asthma, peptic ulcer and rapid heart action, that were especially interesting because of their onset under combat conditions. In general it can be said that these patients, never having dealt adequately with their outgoing forces, — for example, hostility and aggression, — find themselves overwhelmed in a situation of combat that calls up these emotions in such extreme degrees.

It seems that the man who has developed a so-called "war neurosis" was predetermined before he entered the Service. It might even be said that war neuroses are "made in America" and only come to light or are labeled in combat. It is certainly a striking and a most significant fact that the majority of normal soldiers, sailors and marines do not break in combat although they are exposed as long and as fiercely as are those who do. Those who carry on the longest before they break have the best prognosis. The men who arrive at the zone of combat with an attitude of defeat are the ones who break down the quickest, some of them on the first day or after the first few shells or bombs. These are the ones who have the poorest prognosis and do not want to get well. They are "through." The war is over so far as they are concerned, and all they want is to go home. Thus their symptoms acquire a tremendous secondary importance. They are the ones who are always full of complaints, utilize and magnify their symptoms, and are perfectly hopeless so far as any use in the war effort is concerned. The attitude of the patient is more important than his symptoms, and it determines whether or not he

wants to get well and whether or not he wants to fight.

The killing of a "buddy" is of great importance. It appears that every serviceman goes into war with the philosophy, "It can't happen to me." This belief is severely shaken when a man with whom he has so strongly identified himself is killed. In a sense it is "me" being killed, and so the death is intolerable. Many of the men were extremely upset when this happened and were not upset until it did. In many cases it appeared to be the precipitating factor of the illness.

Our time has been almost entirely occupied with examinations, the recording of histories and findings, the making of diagnoses and dispositions, consultations, and the supervision of patients. Therapy has accordingly been limited. The foremost problem was that of anxiety and uncertainty, with restlessness, jumpiness and insomnia. Deeper lying were the attitudes of bewilderment and defeat and hysterical conversion symptoms. The quickest approach to the surface symptoms was through sedation, principally with phenobarbital. On one ward this was made optional and restricted to the night. All the patients were told on admission that sedatives had been ordered for them but would be given only on their request when they were unable to sleep. This was done to avoid the feeling of being dependent on sedatives, — loss of mastery with a wish to be and fear of being overwhelmed, so often the basic conflict in anxiety states, — which itself may give rise to further anxiety and defeat the action of the sedative. The patients were told to use sedation as a man with a sprained ankle would use a cane. On another ward all the patients received sedation, disguised as a tonic, three times a day. The patients did not remain in the hospital long enough for a definite evaluation of these two methods, but the ward where the sedation was given regularly was the quieter of the two. Hydrotherapy was not available. Occupational therapy was instituted as the last third of this group of patients was passing through the hospital. In single cases it was of great value, and it has since grown to fill an important place. Hypnotism was used in a number of cases by one of us (M. M.). This resulted in obtaining the pattern of the underlying conflict in a quick, clear way. It was also useful in clearing up amnesias, anesthetics, paralyses and other hysterical symptoms. In general it was found to be a useful adjunct to therapy of the underlying pathologic emotional patterns.

So far as time permitted, group therapy was employed. This was restricted to one ward, containing about 30 patients. A brief explanation of the nature of their illness was given them in the first interview, with stress on the similarity of their symptoms. In subsequent interviews the patients asked questions that were usually requests for an explanation of their symptoms. At times they tended toward testi-

monial meetings, at first with surprise that others had had experiences so similar. Group feeling was rapidly built up, with a tendency to pattern behavior after the patient who made the most rapid progress. The explanation given was superficial, with emphasis on encouragement. The patients did not remain in the hospital long enough for us to go into the deeper aspects of their illness or to evaluate the efficacy of the therapy.

Because these psychoneuroses had their origin in distortions of personality development, we believe that the only lasting therapy is of the individual type in which an alteration of the personality structure is effected. The first step consists in creating a feeling of confidence between physician and patient, which when it becomes stronger than the fear can be used to help the patient deal with his stronger feelings — in divided doses. Because of his confidence in the physician, anxiety is lessened and the vicious cycle previously referred to is broken or avoided. With a growing feeling of accomplishment in doing this — occupational therapy has similar action — the patient is able to deal with ever-increasing amounts of excitation and thus slowly rebuild his personality — mend the fracture. From one point of view this is a retesting of life situations, with guidance in the direction of mastery that should have been accomplished in childhood by the parents. Early treatment is important before elements of secondary gain — attention, sympathy,

display of symptoms, compensation and so forth — give value to symptoms and create a barrier to treatment. Individual treatment is of course impossible in the war situation because of the large number of cases and the few psychiatrists in proportion to the time required.

For practical purposes the person who has once broken under the stress of battle is no longer able to do combat duty. We believe, however, that much could be done in the matter of rehabilitation, the avoidance of the sense of defeat and failure, and furtherance of the war effort if selected patients could be, as a group, assigned to noncombat duties in keeping with their abilities and maintained under psychiatric supervision with such therapy as could be given.

SUMMARY

The findings from a study of 200 neuropsychiatric cases that occurred under combat conditions are presented, and a statistical analysis is reported.

The usual psychoneurosis, with the underlying faults of the personality, is outlined. The origin of this difficulty appeared to be in the immature interpersonal relation that existed between the parents and the child when the latter's personality was in the formative period.

The limited therapy employed is indicated, and suggestions with regard to further treatment are offered.

MENINGITIS IN CHILDREN*

A REPORT OF TWENTY-EIGHT CASES

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BOSTON

MENINGEAL infection in children is fairly common, and in recent months there has been an increasingly high incidence of the disease,¹ particularly of meningococcal meningitis, in some places approaching the proportions of an epidemic. Twenty-eight consecutive cases of meningitis treated at the Boston Floating Hospital between June, 1941, and June, 1943, are included in this report. This period is chosen because it includes all the cases of influenzal meningitis in which type-specific anti-influenza rabbit serum was used.

It will be seen from Table 1 that the cases in this series fall mainly into three etiologic groups, — namely, 9 cases of influenzal meningitis, 12 of meningococcal meningitis, and 5 of pneumococcal meningitis, — with 2 miscellaneous cases, due respec-

tively to the colon bacillus and to a *Salmonella*. The relative incidence is at variance with figures that show the commonest type of meningitis in children to be tuberculous,^{2,3} and it is at least encouraging to see less of this form of the disease. The cases cover a relatively limited age group: all but 3 of the patients were below the age of three and a half years, and this is in keeping with the lack of preponderance of the meningococcal form. Colon bacillus meningitis is not rare in early infancy,³⁻⁵ although it is at every other age.⁶ Cases of *Salmonella* meningitis are apparently unusual.⁷

Influenzal Meningitis

In the group of 9 cases of influenzal meningitis, the age incidence varied from four months to three and a half years, and in all cases but 1 the patient was admitted to the hospital within five days after the onset of the disease. These two factors — the age of the patient and the duration of the infection

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TABLE 1. Analysis of 38 Cases of Meningitis.

CASE No.	NAME	SEX	AGE	DURATION BEFORE ADMISSION	TOTAL DURATION*	OUTCOME	ORGANISM	DRUG	SULFONAMIDE BLOOD LEVEL, mg. %	SERUM	REMARKS
5064	E. K.	F	1 2/12 yr.	20	50	Died	<i>H. influenzae</i> (Type B)	Sulfathiazole	15.0	6 amp.	Evidence of block
5067	S. D.	M	1 5/12 yr.	4	40	Recovered	<i>H. influenzae</i> (Type B)	Sulfathiazole	1.8	7 amp.	
5347	S. N.	F	1 10/12 yr.	4	24	Recovered	<i>H. influenzae</i> (Type B)	Sulfadiazine	6.0	1 amp.	
5510	D. B.	M	2 10/12 yr.	3	21	Recovered	<i>H. influenzae</i> (Type B)	Sulfadiazine (I.V.)	24.0	5 amp.	
5511	M. B.	F	9/12 yr.	2	7	Recovered	<i>H. influenzae</i> (Type B)	Sulfadiazine (I.V.)	10.5	3 amp.	
5635	M. G.	F	3 6/12 yr.	2	15	Recovered	<i>H. influenzae</i> (Type B)	Sulfadiazine (I.V.)	16.0	4 amp.	
5582	P. H.	M	9/12 yr.	5	13	Recovered	<i>H. influenzae</i> (Type B)	Sulfadiazine (I.V.)	10.6	7 amp.	Otitis media; blood culture positive. Diffuse bilateral bronchopneumonia
6060	N. W.	F	4/12 yr.	1	3	Died	<i>H. influenzae</i> (Type B)	Sulfadiazine (I.V.)	22.8	3 amp.	
6117	S. F.	F	1 10/12 yr.	2	21	Recovered	<i>H. influenzae</i> (Type B)	Sulfadiazine		5 amp.	
5531	W. G.	M	1 11/12 yr.	1	6	Recovered	Meningococcus	Sulfathiazole (I.V.)	17.0	10 cc polyvalent	Meningococcemia; rash
5667	L. V.	M	2 yr.	3	12	Recovered	Meningococcus	Sulfadiazine			Eliminating meningococcemia, with rash. Waterhouse-Friderichsen syndrome; spinal-fluid culture positive.
5512	D. C.	F	7/12 yr.	10	20	Recovered	Meningococcus	Sulfadiazine			Waterhouse-Friderichsen syndrome; spinal-fluid culture negative.
6183	P. M.	M	2 1/12 yr.	3 1/2	3 1/2	Died	Meningococcus	Sulfadiazine			
6387	A. S.	F	9/12 yr.	3 1/2	3 1/2	Died	Meningococcus	Sulfadiazine			
6244	P. K.	F	3 yr.	10	16	Recovered	Meningococcus	Sulfapyridine (I.V.)	34.0		
6278	G. M.	M	1 9/12 yr.	5	8	Recovered	Meningococcus	Sulfadiazine	21.8		
6307	P. K.	F	2 3/12 yr.	3	7	Recovered	Meningococcus	Sulfadiazine	22.4		
6376	D. L.	M	5 yr.	1 1/2	2 1/2	Recovered	Meningococcus	Sulfadiazine	12.8		Rash; blood culture negative; spinal fluid on admission clear, with positive culture; spinal fluid next day cloudy with negative culture.
6464	J. F.	M	9 10/12 yr.	1	5	Recovered	Meningococcus	Sulfadiazine	15.0		Rash
6486	R. G.	M	10 yr.	4	11	Recovered	Meningococcus	Sulfadiazine	14.8		Evidence of block; pacnomia; spinal-fluid culture always positive.
6498	R. S.	M	8/12 yr.	2	8	Recovered	Meningococcus	Sulfadiazine	14.8		
5671	C. T.	M	6/12 yr.	3 1/2	18	Died	Type 7 pneumococcus	Sulfadiazine	18.0	40,000 units	
5948	M. H.	F	1 2/12 yr.	1	14	Recovered	Type 19 pneumococcus	Sulfadiazine (I.V.)	45.0	360,000 units	
6077	M. R.	M	2/12 yr.	3 1/2	12	Died	Type 23 pneumococcus	Sulfadiazine (I.V.)	52.0	140,000 units	Blood culture positive
6226	M. S.	F	8/12 yr.	2	3	Died	Type 4 pneumococcus	Sulfapyridine (I.V.)		40,000 units	Blood culture positive, patient died 17 hours after admission.
6293	C. B.	M	3/12 yr.	6	7	Died	Type 5 pneumococcus	Sulfadiazine and Sulfapyridine (I.V.)			
5136	A. M.	F	6 wk.	14	21	Recovered	Colon bacillus	Sulfathiazole	2.5		Blindness developed owing to optic atrophy.
5130	B. L.	M	5 wk.	14	56	Died	<i>S. oranienburg</i>	Sulfathiazole	8.2		Evidence of block; multiple walled-off abscesses.

* Duration to the first spinal-fluid culture that was sterile or to the day of death.

prior to treatment — seemed to have an important bearing on the outcome. Of the 2 patients who died, one (E. K.) had evidently had meningeal infection for at least twenty days prior to admission, and the ventricular block that occurred had probably developed previously. Because of large amounts of fibrin in the spinal fluid, block is a likely complication of this type of meningitis.⁸ The second patient who did not survive (N. W.) was a four-month-old infant, the youngest in the group. She had apparently had meningitis for only one day prior to admission, but she was highly toxic and moribund and had a diffuse bronchopneumonia.

In the management of these cases an attempt was made to follow a definite plan, such as has been suggested in several recent articles.⁹⁻¹² In all cases the organism was found in the direct smear of the spinal fluid soon after admission and was typed directly from the spinal fluid. The organism in each case was the Type B influenza bacillus; this is true in the majority of influenzal infections in children.^{10, 11} The bacteriologic diagnosis was confirmed by culture of the spinal fluid and the blood. The total and differential cell counts of the spinal fluid indicated the presence, but not the severity, of the meningeal infection, and afforded a convenient means of following the course. The spinal-fluid sugar was usually, but not always, reduced, and usually increased progressively as the infection subsided. The correlation between an extremely low spinal-fluid sugar and an extremely severe infection has been emphasized elsewhere.¹⁰ In these cases the results were too varied to confirm this, and it was thought that the sugar had mainly a qualitative value. The spinal-fluid protein was elevated in every case.

Treatment was directed toward two ends: the general supportive measures required by any acutely ill patient and the specific measures against the infection. Several of these patients were semicomatose and irrational and in moderately severe medical shock, owing to loss of fluids from refusal of feedings, vomiting and so forth, and it was impossible to administer fluids and medications orally. In 7 of the 9 cases, a continuous intravenous injection was started immediately, and everything was given by this route until the patient was able to take and retain things by mouth. Such an intravenous injection usually ran continuously for twenty-four to forty-eight hours, and when necessary a second vein was used. Thus fluids were started immediately and given in amounts that supplied the patient with between 1000 and 15,000 cc. every twenty-four hours, depending on his weight. In these cases it was possible satisfactorily to correct and control dehydration and acidosis with physiologic saline and glucose solutions. Satisfactory results were observed in several cases in which the solutions were alternated — that is, first normal saline solution and then 7.5 per cent glucose in water (which is slightly hypertonic, and can be given safely intravenously).

This was done to avoid the danger of overloading the patient with sodium chloride and producing edema. When shock was present, plasma and whole blood were used, the latter because of the anemia that may develop secondary to infection and to large doses of sulfonamides.

Further general treatment consisted largely of nursing care and symptomatic management of the manifestations of cerebral irritation and elevated intracranial pressure. Convulsions were controlled by sedation: a mixture of equal parts of sodium bromide and chloral hydrate, given as a retention enema, was found to be a helpful sedative, particularly in small infants. The symptoms of excessive intracranial pressure were relieved by lumbar puncture, letting the fluid flow slowly and removing only a small amount at a time. If there was evidence of blockage of the ventriculospinal system, — that is, if only a small amount of fluid was obtained and the symptoms were unrelieved, — cisternal or ventricular puncture or both were done. In most of these cases frequent lumbar punctures were avoided; one was done on admission to determine the diagnosis, and thereafter two or three taps were made to follow the course of the disease.

The specific treatment consisted of the use of sulfonamides in large doses, and of type-specific anti-influenza rabbit serum. The relative benefit of the two types of therapy could not be evaluated because all cases received both sulfonamides and serum.* In all but 2 cases the drug employed was sulfadiazine, because of its relative freedom from toxic side effects,^{14, 15} and because of its purported ability to filter readily through the choroid plexus and produce a relatively high level in the spinal fluid.¹⁴ The drug was used intravenously in all the cases that were admitted after the soluble form of the drug (the sodium salt) became available, and the administration of the drug offered no difficulties; it was simply added at appropriate intervals to the continuous intravenous injection already running. Specifically the dosage for the first few days of illness in these children was between 2 and 4 gr. (0.13 to 0.27 gm.) per pound of body weight, averaging 3 to 3½ gr. (0.20 to 0.23 gm.), given intravenously in a 5 per cent solution. The dose was increased or decreased according to the level in the blood, an effort being made to maintain this level at 10 to 15 mg. per 100 cc. Only 2 of the 9 patients in this group reached levels of over 16 mg., and their recoveries were no more rapid or spectacular than those of any others. As soon as possible the dosage was diminished in every case, and as soon as the patient could retain fluid and drug by mouth the intravenous

*One patient (S. B.) showed a maximum blood sulfathiazole level of 1.8 mg. per 100 cc., lower than that of any other patient, and usually regarded as insufficient to effect therapeutic action of the drug. The fact that he survived speaks for the importance of the serum, of which he received large doses over a long period. On the other hand, encouraging results have been reported with chemotherapy (sulfadiazine) alone.¹⁵

†In a few cases, simultaneous levels were taken in the blood and spinal fluid, and the spinal-fluid levels were found to be between two thirds and three quarters of the blood levels. These findings seem to agree with those of others.^{11, 16}

route was discontinued, usually in thirty-six to forty-eight hours. No serious untoward results from the drug were observed, but experience in this group of cases was limited almost entirely to sulfadiazine. One case has been reported of fatal nephritis from sulfathiazole that developed during the treatment of influenzal meningitis with this drug in combination with sulfapyridine.¹⁷ Reports indicate that results obtained with sulfapyridine have in general been better than those with sulfanilamide.^{18, 19} Whether the height of the blood level of the drug over a certain point has any bearing on the outcome of the treatment is difficult to decide.^{11, 20}

The specific antiserum was given as soon as the bacteriologic diagnosis had been made. Two types of serum are available: horse serum^{8, 21} and rabbit serum.^{22*} All these patients were given rabbit serum, which was injected intravenously and allowed to run into the vein slowly, dissolved in several times its volume of normal saline solution, so that each ampoule (25 mg. of antibody nitrogen) took at least two or three hours to run in. All patients were first skin tested, but no positive reactions were found. From one to three ampoules (25 to 75 mg.) were given the first day, and thereafter the dosage was determined by the actual titer of antibody in the blood, as measured by daily Quellung tests. In the recent cases, the Quellung test was done with the patient's serum in a dilution of 1:10, to ensure the presence of antibody in more than necessary abundance, according to a published suggestion.¹⁰ It has also been recommended that the patient be kept desensitized by giving small doses of antiserum fairly frequently until recovery is assured.²¹ The patients in this group received 4 to 5 ampoules. Two patients who survived were given only 1 and 3 ampoules respectively, and 2 received 7 ampoules each. We have had no experience with this serum given intrathecally. Others^{10, 23} have used this route, and have recommended it particularly when patients fail to show the expected improvement with intravenous treatment alone. In our group the patients showed little clinical improvement before the second or third day after therapy was begun.

Meningococcal Meningitis

The 12 cases of meningococcal meningitis confirmed the opinions expressed in the recent literature regarding the efficacy of sulfonamide therapy in this type of meningeal infection.^{11, 12, 24-29} Except for 2 cases the age incidence was from two months to five years. The duration of symptoms prior to admission varied from one day in 4 cases to ten days in 2 cases, averaging four days. Two patients died, the infection in these taking the form of a fulminating meningococcal septicemia. All the other patients survived, with no specific treatment other

than large doses of sulfonamides, except for one (D. C.) who also received a small amount of polyvalent antiserum.

The management of these patients was less exacting than that of those with influenzal meningitis; many of them did not show the extreme toxicity observed in the influenzal cases. For this reason fluids and medication could usually be given orally from the start, although it was often necessary to supplement the fluid intake with intravenous or subcutaneous injections. Only 1 patient in this group (A. S.) received intravenous chemotherapy,† but high blood levels, from 17 to 34 mg. per 100 cc., were obtained with oral administration. Sulfadiazine alone was used in 9 cases, and the three other sulfonamides in 1 case each. Cases were treated successfully with sulfadiazine, sulfathiazole and sulfanilamide, respectively. In the fatal case (A. S.) treated with sulfadiazine and sulfapyridine the patient actually received little of either. The sulfadiazine was given orally and not retained, and one dose of sodium sulfapyridine was given intravenously, when the patient was already in extremis. The patient in this group who was given serum was so treated because she showed evidence of an acute ethmoid sinusitis, and it was thought possible, but never proved, that this was a focus of the infection.

The 2 patients in this group who died (P. M. and A. S.), both infants, of two and nine months, respectively, had acute fulminating meningococcemia, or the Waterhouse-Friderichsen syndrome.³⁰⁻³² The onset in each case was extremely acute and the course was typically rapid. Each patient was admitted only a few hours after the first symptoms of illness, and the total duration in each case from the onset of symptoms to death was twelve hours. Blood cultures in both cases grew a meningococcus, and this organism was found on culture of the spinal fluid in one case, although the spinal fluid in both cases was negative on microscopic and chemical examination. Autopsy showed in one case complete destruction of the adrenal glands by hemorrhage; in the other there was only a small amount of adrenal hemorrhage. Treatment consisted of intravenous sulfonamide therapy, fluids, plasma and so forth and in one case adrenalin and adrenocortical extract.³³

The opposite extreme is illustrated by the case of a five-year-old boy (D. L.) admitted with possible signs of meningeal infection, a slight petechial rash and a high fever of one and a half day's duration. He was in no distress, was not toxic and complained only of general malaise and headache. The spinal fluid on admission showed nothing abnormal; the cell count was only slightly elevated, the chemical findings were normal, and the smear showed no bacteria. The patient was started on sulfadiazine, however, because of the obvious, if unproved, in-

*Rabbit serum is less likely to produce allergic reactions, and it possesses the theoretical advantage that the antibodies are contained in a smaller protein molecule than they are in horse serum, and thus diffuses more readily through the choroid plexus.²⁵

†At the time of writing, another patient, still in the hospital, received intravenous sodium sulfadiazine for the first twelve hours after admission, and developed a gross hematuria, which cleared up the following day following alkalinization of the urine.

fection, and by the following morning the spinal-fluid culture taken on admission had grown meningococci. Another spinal tap, done that morning, showed cloudy fluid with a marked neutrophilic reaction, but the fluid was sterile on culture. In other words, the patient had been cured within less than a day after chemotherapy had been begun.

Pneumococcal Meningitis

The 5 cases of pneumococcal meningitis indicate that this disease still has an extremely poor prognosis.^{11, 12} Of 5 patients, only 1 survived, although they all received intensive treatment. Recent figures in the literature show far lower mortality rates than this,^{12, 19, 34} but not in this age group. The age incidence varied from two to fourteen months. The patient who survived (M. H.) was the oldest of the group, and was admitted with a typical history of an acute onset of meningitis of one day's duration. There was no apparent focus of infection and no previous illness leading up to the meningitis. She was treated in much the same way as were the patients with influenzal meningitis discussed above; continuous intravenous therapy was necessary for several days, and the patient received large doses of soluble sodium sulfadiazine (3 or 4 gr. — 0.20 to 0.27 gm. — per pound of body weight a day) by this route. In addition she was given large doses of type-specific antipneumococcus rabbit serum intravenously, the dosage totaling 360,000 units, spread out over several days. Repeated Quellung tests with the patient's serum against her own organisms showed adequate antibody titer in the blood. The concentration of sulfadiazine was allowed to rise very high: on the second day after admission it was 45 mg. per 100 cc., and for the ensuing week it was still very high, gradually decreasing as the dose was decreased and the method of administration was changed from the intravenous to the oral route. Clinical improvement was slow. The temperature came down by lysis, remaining above normal for two weeks, and the first sterile spinal-fluid culture was made on the thirteenth hospital day. The patient made a complete recovery and was still free of any evidence of sequelae six months later. She never showed any signs of drug toxicity, despite the sustained high level of sulfadiazine.

An even higher level of the drug was reached in another patient in this group (M. R.) — 52 mg. per 100 cc. This patient died after twelve days of intensive treatment, and at autopsy the kidneys showed no evidence of damage due to sulfadiazine. Levels of sulfapyridine in the spinal fluid up to 50 mg. per 100 cc. have been reported and have been well tolerated.³⁵ As in the cases of influenzal meningitis, it is difficult to evaluate the benefit to the patient of these high concentrations of sulfonamide.

Of the patients in the pneumococcal group who died, 2 showed other (primary) foci of infection. In one case there was an extensive bronchopneumonia,

and in the other an acute otitis media, from which the same type pneumococcus was cultured as the one found in the spinal fluid. Of the 4 patients who died, 2 died within a day after admission, before adequate chemical or serum therapy had been given; the other 2 survived for eleven and eighteen days respectively. Positive blood cultures were obtained in 3 of the 5 cases, including the patient who survived.

No conclusions can be drawn from this group other than that the disease is so serious that the most intensive therapy is demanded. Sulfonamides have had an important part in lowering the mortality of this disease,^{11, 36, 37} but the consensus is that the combination of sulfonamide and serum therapy offers the best chance for recovery.^{35, 38-43} This is probably particularly true of the age group dealt with in this paper.

Colon-Bacillus and Salmonella Meningitis

Two other cases complete this series. One was that of a six-week-old infant with meningitis due to the colon bacillus. This patient responded well to treatment with sulfathiazole, with a maximum concentration in the blood of 2.5 mg. per 100 cc. The spinal culture became negative within a week, and the clinical course was uneventful, except for atrophy of the optic nerve, which produced blindness. Such neurologic changes are relatively common among patients who survive colon-bacillus meningitis.⁴

The other case was that of a five-week-old infant with meningitis due to a member of the *Salmonella* group.⁴⁴ These organisms are rare as a cause of meningitis,^{3, 7, 45} not more than 41 cases being reported in the literature.^{7, 45-48} The organism in this case was identified as *Salmonella oranienburg*, one of the paratyphoid C or cholerae-suis group. It is described as not normally being pathogenic for mammals,⁴⁹ and it has usually been found in birds, particularly chickens and pigeons. It has been recovered from human beings in cases of gastroenteritis^{50, 51} and food poisoning.⁴⁹ The patient came from a farm outside of Boston, but attempts to recover the organism from the livestock on the farm were unsuccessful. This organism has been identified as the cause of meningitis in one other case.^{51, 52}

The patient's course was steadily downhill. He failed to show any response to sulfathiazole,* in spite of a blood level of 8.2 mg. per 100 cc. He developed signs of blockage of the ventricular system, with a progressive increase in the head circumference despite almost daily cisternal or ventricular taps. At autopsy there was practically nothing left of the brain tissue itself, and there were large walled-off sacs of pus throughout the brain.

SUMMARY

* Twenty-eight consecutive cases of meningitis are reported, and the treatment is described. In in-

*In the past, *Salmonella* meningitis has been considered a usually fatal disease,⁴⁶ but recent reports show cures with the use of sulfonamides.^{7, 45, 53}

fluenzal and pneumococcal meningitis, the combination of specific antiserum and sulfonamide was used, this appears to be the most effective treatment. In meningococcal meningitis, sulfonamide therapy alone was used, this is apparently sufficient to effect a complete cure, except in cases of fulminating meningococcal septicemia.

The case mortality in this series was as follows in the cases of influenzal meningitis, 2 patients out of 9 died. In the cases with meningococcal infection, 2 patients out of 12 died, these were both infants with acute meningococcemia and the Waterhouse-Friderichsen syndrome. In the cases of pneumococcal meningitis, 4 patients (all under eight months of age) out of 5 died. Of the others, 1 survived with colon-bacillus meningitis and developed blindness as a sequela, and 1 died with meningitis due to *Salmonella oranienburg*.

We are indebted to Drs Elmer W Barron, Theodore Bennett and Francis C McDonald for permission to include in this series a private patient of each.

20 Ash Street

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Correction. In the paper "Dicumarol Therapy in Thrombotic Emergencies" by Dr Evans, which appeared in the February 3 issue of the *Journal*, in Table 2 under the column "Subsequent Embolism" opposite "Venous thrombosis or embolism complicating previous operation" the figure "1" should be "0" and the "total" should be "1" rather than "2."

MEDICAL PROGRESS

NEW THEORIES CONCERNING ASTHMA

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RECENTLY there came to the Massachusetts General Hospital a patient whose case illustrates so many of the problems concerned with asthma and emphysema that it will be helpful to use it as a text for the following review of the facts and theories of this disease.

The patient was an active lawyer and business man of fifty-two who through most of his life had been well except for a troublesome nasal catarrh, which continued without change in different seasons and environments. There was no history of eczema or of seasonal hay fever, and there was no asthma until the age of forty-seven. At that age, the nasal catarrh became worse and sinusitis developed. The patient began to cough at night, and his appetite fell off. He began to lose weight. He was run down and was sent to Hot Springs, Arkansas, for rest and treatment. During that visit the asthma first appeared, in a sudden sharp attack. In the five years since then it has continued through all seasons and in all places, with ups and downs perhaps but with no real letup. During this time the patient has had all manner of treatments, as will be discussed.

At the present time he has asthma and emphysema of a severe grade. The chest has a barrel shape, but there is no clubbing of the fingers. The air sacs are distended, and one can assume that many have coalesced to make larger air spaces, with consequent reduction in the surface area of the lungs. The diaphragm is low and under the fluoroscope it moves but little. The function of the lungs is greatly reduced. There are times, however, when the patient can lie back on his pillows comfortably and can walk to the toilet without trouble, but there are other times when mucus collects in the pharynx or bronchi or both and precipitates a violent attack of cough and wheezy dyspnea. This is relieved somewhat by an epinephrine spray and better by adrenalin given subcutaneously, but occasionally requires an intravenous injection of aminophyllin. It is evident that the disturbance of lung function is not constant in degree, and it is hard to believe that all these symptoms can be explained simply by the mechanical limitation of this function.

The patient is generally miserable. He is evidently frightened by his disease and is obviously apprehensive about its future developments. He has lost much weight, is very thin, and has no appe-

tite. He is unable to concentrate on anything and he does not care for reading.

What causes this disease? The wheeze suggests allergy, but it is now recognized that "all is not allergy that wheezes," and in this case, as in many of similar nature, it is not possible to demonstrate any relation between the symptoms and changes in the environment or diet. The patient has lived in different places, but he could never see that houses, rooms, mattresses or pillows made any difference to him.

One thinks of foods. Here in the hospital he was fed a diet high in calories and vitamins, with no limitation as to choice of foods, and seemed to thrive on it. Skin tests were made on three different occasions by three different physicians, and it is interesting to compare the reports. There are one or two items that appear in each of the reports, but on the whole the "foods allowed" and the "foods to be avoided" vary within considerable limits. Furthermore, diets have been arranged on the basis of these previous tests; the patient has followed each of them closely but without benefit. At one time the diet was limited to fruit juices and gelatin, with several enemas a day, and the patient said that the procedure "nearly killed" him.

Eosinophils in blood smears have reached 13 per cent and once 20 per cent of the total leukocytes, which have run to 10,000 and 12,000 per cubic millimeter. This eosinophilia is suggestive of allergy, but there is no reason to assume that allergy is its only cause.

The theory of allergy fails to explain this type of case. The onset at the age of forty-seven was late for the development of hypersensitiveness. More important is the fact that the symptoms bear no relation whatever to changes in season or environment.

Is the patient "toxic"? His voice has a nasal quality. He has trouble in the sinuses as well as in the bronchi. The sputum is considerable in amount but consists only of frothy mucus. It is not purulent. There is no fever, and the white-cell count is not elevated. The evidence of toxicity from bacterial action is not so marked as in other patients who are less miserable.

Operations on the sinuses in patients with asthma have been discussed for years. Some writers claim to have cured their patients by operation, and no doubt such good results do occur. On the other hand, other writers hold that the sinus disease is a

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part of the picture and not the cause of it. The literature on this subject has been reviewed well and completely by Hansel.¹ The incidence of asthma in nasal and paranasal sinus disease, according to him, varies from 3 to 22 per cent, and that of gross nasal disease in asthma varies from 20 to 90 per cent. The results of rhinologic operative treatment of asthma show "cures" (the word is always quoted) in 5 to 20 per cent of the cases, although two of the papers cited by Hansel gave higher figures for small series of patients. Meantime the figures for "good results" additional to the "cures" vary from 10 to 80 per cent. There are, however, a large number of patients with a history of previous operations of various kinds and yet without benefit from them.

Weille² in 1933 made a complete study of 40 patients with sinus disease and asthma. They had been selected for operation with the greatest care and were followed for at least two years after operation. Only 4 patients were made free of their asthma, but 8 others were markedly improved and 6 obtained moderate improvement. Eighteen cases, however, were failures, except that 7 of them were cured or improved for a few months. More recently Cooke,³ in discussing the allergy problem, mentioned that he and Grove had treated a large number of patients by sinus operation. Of those with adequate sinus surgery, only 8 per cent remained unimproved, whereas of those with incomplete surgery, 64 per cent were unimproved. The difference is impressive.

The paranasal sinuses consist of collections of bony cavities, some small and tucked away in remote places. The difficulty of evacuating the contents of every one of them is understandable. One trouble with the theory that good results follow only those operations that are adequate is that in a number of cases the asthma has been cured or improved when no operation at all was performed, or when only one side of the nose was treated — and these patients had aside from asthma all the earmarks of chronic sinus disease. Whether there is a special way of performing sinus surgery — whether, for example, the good result depends on the chance excision of a particular sensitive spot, or perhaps of a certain nerve ending — is a question not yet answered. In recent months the practice at the Allergy Clinic of the Massachusetts General Hospital has been to operate only when the condition of the sinuses is so bad that operation is indicated without regard to the asthma. As patients who have been operated on either outside or in our clinic are observed, it becomes more and more clear that sinus surgery does not often effect a cure.

The patient described above, for example, has already had three operations. The first was for the removal of polyps. The second was performed in March, 1942, in the fourth year of the asthma. On the morning after it, his wife went to see him in the hospital and found him unconscious and cyanotic. Fortunately meningitis was recognized and treated

at once with large doses of sulfonamide drugs, and the patient recovered. He was in the hospital for three months. Whether the so-called "polyp" that the surgeon saw was a meningocele with direct connection to the cranial cavity, or whether the curet was pushed through an extra thin plate of bone, is hard to say; the accident shows well that extensive sinus surgery can be dangerous. The asthma cleared during this emergency, but it returned before the patient left the hospital, and the next winter he went back to Arizona, where the asthma persisted but he gained a little strength.

In June, 1943, emphysema was marked and asthma was troublesome. Epinephrine by hypodermic injection gave some relief. Aminophyllin by mouth (3 gr. three times a day) seemed helpful, but aminophyllin by vein (in an ampoule containing $3\frac{3}{4}$ gr. dissolved in 10 cc. of normal saline solution) was at times necessary. The sinuses were cloudy as shown by x-ray and another operation was performed. Nasal polyps were removed and windows were cut on each side between the nasal cavity and the antrum. There was a little improvement for a week or so but the asthma then returned as before. The latest x-ray films still show thickening of all the sinus membranes, but it is clear that no one wishes to operate again on the nose or sinuses.

There is no report that deals directly with bad teeth as a cause of asthma, although hundreds, if not thousands, of teeth have been removed in the hope that the cause of trouble would be removed with them. In several cases at the Massachusetts General Hospital abscessed teeth have been removed, but obviously without benefit. In a few cases, however, the results have been almost miraculous, so that chronic asthma with a short duration and a severe course, as in the case here described, has been greatly improved when abscessed teeth were found and extracted. In this case x-ray films did show small abscesses around several of the teeth, and six of these were extracted. There was a reaction, consisting of a moderate increase in the asthma on one day.

Has this patient some organic lesion in the bronchial tree that is causing his asthma? This question should be asked in all cases, for carcinoma and other tumors of the bronchial wall may occur. I have seen several such cases. Sarcoid disease and tuberculosis have also been obvious, with lesions on the bronchial mucosa producing local irritation in rare cases. A syphilitic gumma was found in another case. In each of these, however, the lesion was shown by x-ray. In the present case, the x-ray films are remarkably free of any evidence of a local process.

The nervousness can be easily explained as a result of the disease rather than as a cause of it. When later in the hospital stay the symptoms improved, the nervousness also subsided. In his recent book *The Borderlands of Psychiatry*, Cobb⁴ shows most wisely that disturbances of the psyche are not to

be separated sharply from those of the general bodily function. In diseases of every kind and in almost every patient, some evidence of psychic abnormality can be found. Psychic disturbances are to be expected whenever symptoms are severe, but in most cases, as in this one, an explanation of the trouble on the basis of nervousness alone is not sufficient.

So far, no one of the ordinary theories concerning the cause and nature of asthma applies to this case, and the same statement can be made for many other cases in the same group. One has to think of some physiologic disturbance the nature of which is so far unknown. Albright⁶ says, "Obscure diseases usually are not made lucid by incriminating the endocrines." Nevertheless in the present case, as in others like it, there is some evidence of abnormality in the function of the adrenal glands.

First, however, a word must be said about epinephrine, the active secretion of the adrenal medulla. Adrenalin relieves asthma. It relieves this patient at times, but not so well as it relieves the more typical extrinsic cases. Has the patient a deficiency of adrenal secretion, or has he perhaps lost the ability to respond to it in the normal fashion? Bloor and Bullen^{6,7} have described a chemical method for determining epinephrine in the blood. Normally in dogs and human beings, the presence of epinephrine cannot be demonstrated in the peripheral venous blood. When various solutions of epinephrine were injected intravenously and in large quantities (as much as 1 cc. of a 1:1000 dilution) into a 30-pound dog, 25 per cent was recovered in one minute, 21 per cent in five minutes, and 14 per cent in twenty minutes after the injection; the remaining 40 per cent was lost.

Koref and Rivera,⁸ also using a colorimetric method, attempted to study the epinephrine content of the adrenal glands after the administration of histamine and of peptone and after anaphylactic shock, but in their preliminary work the values for normal animals and man varied widely, with a tendency toward lower quantities in older people. Cohen, Rudolph, Wasserman and Rogoff⁹ found no significant alteration in the rate of secretion of epinephrine from the adrenal glands of sensitized dogs before and during anaphylactic shock from horse serum. There are no studies of adrenaline in the blood in asthma, and it seems unlikely that such a study would be profitable. The physiologic activity of epinephrine is so great that one can ascribe its therapeutic effect to a direct stimulation of the sympathetic nervous system rather than to an indirect replacement of the hypothetical insufficiency of the secretion of the adrenal medulla.

The adrenal cortex is quite another matter. Three functions of it have so far been recognized. The first is concerned with the metabolism of salt and water. This is markedly deficient in Addison's disease and can be improved by treatment with desoxycorticosterone. The second is concerned with the sugar

metabolism and influences the formation of sugar in the body from the breakdown of protein substances. This function is expressed by Compound E of Kendall,¹⁰ which is described as 17-hydroxy, 11-dehydrocorticosterone. Albright¹¹ calls it the S hormone (see below). The third function is concerned with nitrogen, with growth and with the building of protein. It can be estimated in part by the determination of the amount of 17-ketosteroids excreted in the urine. Albright calls it the N hormone.

There are a number of clinical observations in asthma that suggest disturbances in the salt-and-water metabolism. Potassium iodide is of benefit, supposedly because it stimulates the mucous glands in the bronchi. Bloom¹² has recommended potassium chloride for hay fever. Does the potassium radical have any other action? For some patients I have prescribed teaspoonful doses of bicarbonate of soda after each meal, to be taken with the potassium iodide, and some patients like it. To others I have given hydrochloric or nitrohydrochloric acid, as advised originally by Beckman,¹³ and some of them like this. When asthma is extremely severe and the patient is in great distress, the intravenous injection of 1500 cc. of normal saline solution containing 5 per cent glucose is usually effective. The dose provides about 14 gm. of sodium chloride and about 45 gm. of sugar; it is sometimes repeated in six to twelve hours. When patients with severe asthma develop cor pulmonale with edema of the extremities, the asthmatic wheeze usually ceases. Incidentally, the fact that asthma clears during fever and during jaundice is also interesting. These clinical observations suggest that the administration of extra salt does good. There are several papers that touch on this subject, but they give the opposite impression—namely, that extra salt does harm.

In 1940, Stoesser and Cook¹⁴ observed that the feeding of large amounts of dextrose to children with asthma helped them, but if large amounts of sodium chloride were given at the same time, the total effect was not so good. In another paper, the same authors¹⁵ described a new experiment. Children were placed on a diet low in salt. They lost water and weight, and when they were dehydrated fever therapy helped the asthma. If, however, sodium chloride was fed, water was again retained, and when the salt content of the serum returned to normal, fever therapy no longer relieved the asthma. Pitressin was tried because this hormone from the posterior pituitary gland has an antidiuretic action. It can cause a retention of water without the retention of sodium chloride at the same time. A child was placed on the same low-salt diet and continued to have asthma. On the eighth day Pitressin was given and the water intake was considerably increased. After twenty-four hours the asthma cleared, and in thirty-six hours the patient had gained 1.5 kilograms in weight. The treatment was then stopped; the patient excreted 2000 cc. of urine in twelve hours, but the

asthma did not return. After a few months, however, when the sodium chloride content became high, asthma again appeared. Another child also continued to have asthma on a low-salt intake and was benefited by Pitressin. During the antidiuretic phase caused by the drug, water was retained and the asthma cleared, but later when the Pitressin was withdrawn and diuresis occurred, the wheezing recurred. In observations made by Stoesser and Cook on 20 children, in 18 the asthma improved during the phase of water retention, and with it there was a drop in the concentration of sodium, potassium and chloride in the serum. Data on the actual excretion of electrolytes in the urine are not given, but other studies indicate that salt is lost to the body in the more concentrated urine of the antidiuretic phase of the effect of Pitressin. The authors conclude, "It is apparent that bronchial asthma can be ameliorated even in the presence of excessive hydration if there is an associated depletion of sodium chloride." Donovan and Harsh¹⁶ compared the concentration of serum sodium in normal and in allergic persons and found the figures to be about the same. In pregnancy they were a little lower than the average, suggesting that asthma is less severe during pregnancy because of the depletion of electrolytes.

Of greater interest is the paper by Sheldon, Howes and Stuart.¹⁷ They were fortunate in having 5 patients in whom asthma could be started and stopped by exposure to specific foods or dusts. These patients were placed on constant diets with a fixed water intake and the allergenic food was then fed. During the attack that ensued there was a marked loss of water and sodium, so much so that the sodium excreted in the urine was increased to twice the quantity eliminated during the nonasthmatic period. During the asthma the total quantity of sodium excreted in the urine in twenty-four hours was 3 to 5 gm. more than the amounts ingested. In the discussion of this paper, it was pointed out that in serum disease, as well as in pneumonia and other diseases producing fever, the body does not eliminate salt and water; the contrast between the findings of Sheldon in asthma and the findings in pneumonia is interesting. This difference in the salt metabolism of the two conditions is hard to explain, but the marked loss of water and sodium during the attack of asthma that Sheldon describes fits well with our own clinical observations, and makes the relief of symptoms by replacing this loss understandable.

Loeb¹⁸ has described the relation between the adrenal glands and salt metabolism. In Addison's disease, the sodium content of the blood is low. A diet without sodium may bring on the symptoms of Addison's disease (adrenal insufficiency), which are relieved when sodium is again given. When the adrenal glands are removed from an animal, there is a tremendous excretion of sodium in the urine, and during this process potassium is retained in the body. The contrast between the loss of sodium and the

retention of potassium is striking. In diabetes and in the ketosis of starvation, on the other hand, the loss of base entails a loss of both sodium and potassium at the same time. When adrenocortical extract in the form of desoxycorticosterone acetate is fed to adrenalectomized animals, the effect is the same as that of giving large quantities of salt (sodium) and water, except that the improvement is more striking. The administration of desoxycorticosterone or its esters to patients with Addison's disease causes a striking retention of salt and water; one of Loeb's patients gained 11 kilograms in the first ten days of such treatment. The concentration of potassium in the blood falls as that of sodium rises.

This treatment, however, is not without danger. When desoxycorticosterone acetate (Doca) was fed to normal dogs, they developed in ten days a sort of diabetes insipidus. They drank water avidly, sometimes 3000 to 5000 cc. a day, but this stopped when the drug was omitted. If continued, however, it brought on a curious weakness of the muscles, and if it was still continued, the animals died in ten to fourteen days. If they were given a 0.15 per cent solution of potassium chloride instead of tap water, the muscle weakness did not occur, although the diabetes insipidus was unaffected. After death the skeletal muscles showed a large amount of sodium and little potassium, and it is clear that the feeding of potassium tended to prevent the decrease in cellular potassium without, however, making any change in the high blood sodium. Evidently the diabetes insipidus depends on the high concentration of sodium in the serum and in the extracellular fluid, whereas the muscle weakness depends on the loss of potassium in the cells and its replacement by sodium. Desoxycorticosterone acetate has a direct effect on the metabolism of electrolytes, but none on that of sugar or nitrogen. Thorn and his associates¹⁹ have shown that other and closely related steroids are concerned with these other processes.

The treatment of asthma with extract of the adrenal cortex has been attempted. In 1936, Wilmer and Miller²⁰ treated patients with an extract of whole adrenal cortex (Eschatin) and claimed results that were spectacular in some cases, although disappointing in others. Fineman²¹ treated 4 patients with Eschatin when their asthma was stationary. One showed marked, 1 moderate and 1 only slight improvement, but in 3 patients there was a decided increase in strength and appetite, with a gain in weight. Nothing is said about the factors of salt and water. Cohen and Rudolph²² used another product of the adrenal cortex (Interrenalin) and found no effect in 4 cases. More recently, Dragstedt, Mills and Mead²³ found that a prior administration of adrenocortical extract to sensitized dogs did not prevent anaphylactic shock but tended to diminish the severity of the reaction. One wonders about the so-called "nonspecific effect" of the doses. In 1938, Prickman and Koelsche²⁴ treated 16 asthmatic pa-

tients with Cortin injected intravenously, and the treatment was supplemented by excessive amounts of sodium chloride given by mouth. Little or no specific benefit was observed.

More recently, the effect of feeding extra salt has been tried on debilitated patients in the Allergy Clinic at the Massachusetts General Hospital. Patients with asthma have been given up to 12 gm. additional of sodium chloride by mouth each day. In some cases, particularly when the patient is thin and in poor general condition, the extra salt has had a good effect, but in others, especially in those who are well nourished and in good condition, no benefit has been obtained. It goes without saying that in this type of experimentation clinical results without actual measure of the effect of treatment mean little. Nevertheless, the results are suggestive. In the case reported herein the chloride content of the fasting blood was 95 milliequiv. per liter in place of the normal figure of 105 milliequiv. The patient felt a little better under the salt treatment.

Another theory about asthma is interesting. Periarteritis nodosa is a pathologic lesion that is occasionally found in patients with severe asthma. In the series of 50 fatal cases reported by Rackemann and Mallory²⁵ in 1940, periarteritis nodosa was found in 5 cases, a high percentage. In 1942, Rich²⁶ reported that the lesions of periarteritis nodosa could be observed in certain patients who died of some acute infection but had serum disease at the same time. Later he and Gregory²⁷ demonstrated that the same results can be produced in rabbits by treating the animals in various ways with foreign serum. This work is an important advance. It shows that periarteritis nodosa is not a disease entity but is merely a part of a complex process, and that the lesion can be produced by methods similar to those used in producing serum disease or the Arthus phenomenon.

During 1943 Selye and Pentz²⁸ presented new data that are likewise of primary importance. They showed that the lesions of periarteritis nodosa, of malignant hypertension and of rheumatic arthritis in rabbits are similar and that each of them can be produced by treatment not only with foreign serum but with foreign proteins of other sorts, as well as by bacterial products. Also, treatment of the animals with desoxycorticosterone acetate together with a large intake of salt produced the lesions of periarteritis nodosa. In discussing their results these writers point out that in each case the lesions depend on treatment that is drastic and produces a profound disturbance in the animal, and they propose the interesting theory that the lesion results from nothing more than the "alarm reaction," a term which was used first by Selye²⁹ in 1936 to indicate the shocklike syndrome that develops from any severe insult to the body. It perhaps depends on excessive secretion of adrenal hormones, but it now appears that treatment with serum, other foreign

proteins or bacteria serves to elicit the alarm reaction in a purely nonspecific manner, and that the development of periarteritis nodosa is merely the response to this severe treatment. Not much is said by Selye about the symptoms displayed by his animals. Asthma is not mentioned, and perhaps it is too much to consider his observations as having any relation to the asthma problem. On the other hand, they are, like the salt experiments, suggestive.

The patient here described suffers from a sort of exhaustion. He has lost weight, the blood pressure is low (110 systolic, 80 diastolic), the pulse is rapid (90 to 100), and the fasting blood sugar is low (73 and 85 mg. per 100 cc. on different days). The glucose tolerance, however, shows a normal curve. The blood protein is 6.6 gm. per 100 cc. In twenty-four hours he excreted only 5.5 mg. of 17-ketosteroids in the urine, whereas the normal man excretes about 15 mg. He is obviously depleted in various ways. This condition suggests a deficiency of the adrenal cortex. Obviously, there are many difficulties in the way of proving that this idea has significance in the asthma problem as a whole. Selye defined the alarm reaction as "the sum of all biological phenomena elicited by sudden exposure to stimuli to which the organism is quantitatively or qualitatively not adapted." Biologic phenomena develop in asthma of every variety, but the very fact that some evidence is in favor of the theory and some against it shows that the alarm reaction by itself has little to do with allergy or with asthmatic attacks that occur as isolated episodes in persons who are otherwise in good general health. At least the consequences of the alarm reaction are not important in average or ordinary cases. When, however, the attacks are repeated or when they become successive and confluent, as in this case, there may be evidence of a general disturbance of severe grade, which, as here, causes symptoms of another kind that are additional to the difficult breathing of asthma. These symptoms are separate from the asthma, even though they are caused by it in the first instance.

Selye's concept of the alarm reaction is most interesting. He shows that the disturbance can develop from injuries of many kinds and without any one exciting cause. The evidence of adrenal activity in the shock stage is followed by other evidence of adrenal exhaustion in the countershock stage, and one might describe this patient as being always in the countershock, depressed phase of the alarm reaction. Albright³¹ has pointed out that the hypertrophy of the adrenal cortex in the alarm reaction is associated with an initial release of the adrenal hormone that controls the production of sugar from protein breakdown (gluconeogenesis), — the S hormone, — and also of the other hormone concerned with the building of protein tissue, — the N hormone, — but that this change is followed by an overproduction of S hormone and an underproduction of N hormone. After injuries the

obilization of energy and the conservation of aterial for general repair are beneficial. On the her hand, if the excess of S hormone and the minution of N hormone are continued too long, generalized debility results. The negative nitrogen alances observed during the alarm reaction, even the presence of an adequate protein intake, come explainable on the basis of a decreased protein synthesis rather than of an increased protein breakdown. The observations made so far in the resent case fit such a theory well, and the conception as a whole should stimulate greater interest in the theory that certain forms of the symptom omplex that is called asthma may be after all merely one expression of a fairly general and diffuse hysiologic disturbance. The treatment of this isturbance by the use of appropriate hormone-like substances that have been developed from investigations based on these theoretical considerations may be expected.

Once more, it is clear that "all is not allergy that heezes."

53 Beacon Street

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

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CASE 30101

PRESENTATION OF CASE

A thirty-seven-year-old trainman entered the hospital because of upper abdominal and periumbilical pain.

The patient was in apparent good health until two or three years before entry, when he noted mild attacks of sharp stabbing pain in the upper abdomen. The pain usually started above the umbilicus and then radiated to the lower part of the chest, through to the back, and down to the lower abdomen. These attacks came on any time of the day without relation to meals or activity, and lasted from a few minutes to two or three hours. They did not incapacitate him. About six months prior to admission the attacks became more frequent and the pain quite severe. They were accompanied by an intense desire for food, which disappeared as soon as he had eaten a few mouthfuls. He developed constipation without any change in the color or consistence of the stools. These symptoms progressed until admission. There were no chills, fever, jaundice, nausea, vomiting or clay-colored or tarry stools. He had lost 20 pounds in weight in three months. He seemed to be constantly hungry.

Physical examination showed a thin, rather pale man who looked uncomfortable but was not in distress. The heart and lungs were normal. Marked tenderness was elicited in the epigastrium, more on the right, with spasm and a suggestion of an indefinite epigastric mass.

The temperature was 99.6°F., the pulse 90, and the respirations 20. The blood pressure was 120 systolic, 90 diastolic.

Examination of the blood showed a red-cell count of 5,000,000, with 80 per cent hemoglobin. The white-cell count was 8900. The urine was negative. The blood sugar was 123 mg. per 100 cc., the non-protein nitrogen 23 mg., and the blood protein 7.2 gm. The chloride was 100.2 milliequiv. per liter. A glucose tolerance test revealed a fasting sugar of 145 mg. per 100 cc.; at the end of the first hour the blood sugar was 193 mg., at two hours 253 mg., and at three hours 235 mg. The serum amylase was

*On leave of absence.

normal. A blood Hinton test was negative. Graham test was essentially negative.

A gastrointestinal series showed a normal esophagus and stomach. The antrum of the stomach was displaced upward and anteriorly by a large mass that seemed to fit into and widen the duodenal loop (Fig. 1). The mass compressed the duodenum but did not obstruct it. Numerous flecky areas of calcification were seen in the mass. Some of these extended farther up into the left upper quadrant. The mucosal pattern of the duodenum was normal.

On the twelfth hospital day a laparotomy was performed.

DIFFERENTIAL DIAGNOSIS

DR. OLIVER COPE: A mass in the region of head of the pancreas is described in the x-ray report. Careful examination of the x-ray films is going to be important in arriving at a final diagnosis, but before seeing the films I shall make certain comments.

The patient's symptoms do not offer a clue as to the nature of the disease. Any mass in the region described could cause such pain. Hunger relieved by food is also not specific of any lesion. The absence of change in the character of the stools suggests that there was no blockage of the pancreatic duct, because if pancreatic lipase is excluded from the upper intestine, the stools usually are grossly fatty. The absence of jaundice excludes blockage of the common bile duct.

The laboratory examination is of some help for points to disease of the pancreas. The important positive finding is a diabetic tendency, the glucose tolerance being decreased. This tendency suggests destruction of islet-cell tissue. Such destruction is unusual but can occur as the result of long-standing inflammation.

The fever on entry apparently did not continue and the process presumably was not infectious. A normal blood amylase does not exclude an inflammatory process: the characteristic finding of a pancreatitis is an elevated blood amylase, but activity of this enzyme has usually returned to normal after the first week of the disease and continues normal during the chronic and late stages of the disease. An elevated blood amylase occurs for a brief period immediately following an obstruction of the pancreatic duct, but does not follow slow, delayed closure of the duct. Complete obstruction of the pancreatic duct is therefore excluded by this normal finding, and one must look for a chronic inflammatory change in the body or wall of the pancreas without demonstrable alteration in the amylolytic power of the blood.

Before we go farther I should like to see the x-ray films. What does the x-ray department mean by an "essentially negative" Graham test?

DR. LAURENCE L. ROBBINS: I think what was meant by the interpretation of "essentially negative" is the lack of evidence of gallstones and the fact that

The gall bladder appears to function well in the Graham test. It is displaced. That is why "essentially" was put in the report.

DR. COPE: It also says that the calcified areas were seen in the region of the mass. Is the mass visible on the films?

DR. ROBBINS: The gastrointestinal examination shows a pressure defect on the greater curvature side of the antrum and in the pyloric region, with definite

determined from the position of the ligament of Treitz.

DR. COPE: Do the areas of calcification retain a constant position in the two examinations?

DR. ROBBINS: Yes.

DR. COPE: Is there no evidence of shift?

DR. ROBBINS: No.

DR. COPE: The first question that comes to mind is, Are these areas of calcification pancreatic stones?



FIGURE 1. Photomicrograph of the Krukenberg Tumor.

displacement of the duodenal cap and second portion to the right, and numerous flecks of calcification in the region of the mass. The mass appears to be fairly well localized to the head and body of the pancreas. The duodenum in the region of the ligament of Treitz does not appear to be displaced appreciably. There is no evidence of invasion of the mucosa of the duodenum.

DR. COPE: "Some of these extended farther up into the left upper quadrant." What does that mean?

DR. ROBBINS: There are areas of calcification in the upper quadrant, but no appreciable enlargement of that portion of the pancreas so far as can be

I think Dr. Robbins will answer "No." I suspect that they are not pancreatic stones, even though the area of distribution involves the pancreas, because the area involves an enlarged pancreas. It is enlarged beyond that which I would suppose could be associated with calculi in the duct of the pancreas. Perhaps these little objects that are in the region of the tail of the pancreas could be explained as stones, but probably not those in the head of the pancreas. Pancreatic stones are rare and perhaps they do occur within the ducts in the presence of an enlargement of the pancreas. I have never seen this. I tend to exclude stones, however, as the primary lesion in

this case on the basis of the circumferential arrangement or pattern. Whether there were stones out in the tail of the pancreas I do not know.

Will Dr. Robbins comment on that?

DR. ROBBINS: Those in the tail might be stones, but the areas of calcification in the region of the head are quite linear and do not have the typical appearance of the few cases of pancreatic lithiasis that I have seen.

DR. COPE: I shall go back one step to say that I think this mass visualized by x-ray with the areas of calcification adequately explains the patient's symptoms and also, one could imagine, the decreased glucose tolerance or inadequate production of insulin. The problem therefore resolves itself into trying to judge the nature of the lesion giving rise to this x-ray picture. Stones can produce a diabetes because there is an associated fibrosis of the pancreas, which results from chronic blockage of the pancreatic ducts, and that fibrosis may go on to cell destruction of the islets with a resultant inadequate amount of insulin. The occurrence of diabetes following stones and fibrosis has been reported. I have never seen diabetes come on following tumor of the pancreas and this seems unusual to me. Yet I suppose it could occur with any slowly growing, fibrosing, sclerosing lesion. Ordinarily if there is a tumor or a cyst that arises in the head of the pancreas and is large enough to block off the duct of the pancreas, there is an atrophy and some sclerosis of the acinar tissues distal to the lesion. But there is usually adequate islet-cell tissue for normal insulin formation.

Did this tumor involve the entire pancreas? No, it did not. Apparently it involved the head, but there is also evidence of some change in the tail. Again, I think this is consistent with the picture. What could it have been if it was not stone in the pancreatic duct? It may have been any one of a large variety of conditions. The commonest are simple cysts and tumors. It is surprising that this man had not had any jaundice, but I suppose the reason is that the distortion of the duodenum was such as to allow free drainage of the common bile duct into the duodenum. The ampulla was probably above the area of pressure. The collapse of the gall bladder in the Graham test bears out the free drainage into the duodenum. Free bile drainage does not exclude obstruction of the pancreatic duct, but a cyst of this size could not be expected from simple obstruction of a pancreatic duct.

The mass could be a papillary cyst arising in a papillary adenoma or it could be one of the simple cysts. A dermoid has to be considered for they occur in the pancreas, but I do not believe that these areas of calcification are the typical markings one would expect in a dermoid. Therefore I shall assume that the calcification had occurred in areas of the cyst or tumor in which necrosis had accompanied the progressive, slow growth of the lesion. Because the calcification points to slow growth I shall assume

that the mass was not malignant and I believe that it was either a cyst, simple or papillary, or a cystic tumor, — rather than a solid tumor that had given rise to obstruction of the pancreatic ducts, — probably with some fibrosis and secondary calcification and, finally, with decreased insulin production.

DR. CHESTER M. JONES: I should like to ask whether prolonged partial obstruction of the pancreatic duct tends to stone formation. It is a rare condition. I have a hazy idea of pancreatic calculus. The diagnosis is usually by exclusion, and we are very apt to be wrong when we make it. Do you know about the formation of stones, Dr. Cope?

DR. COPE: I have no knowledge. I am saying fibrosis and stone from obstruction on a hunch. There seem to be two configurations in the x-ray film, a circular tumor and something behind in the tail. Stone formation is a pure guess. In dog fibrosis regularly follows ligation of the pancreatic ducts.

CLINICAL DIAGNOSIS

Pancreatic cyst.

DR. COPE'S DIAGNOSIS

Pancreatic cyst or cystic tumor with degeneration and calcification (nonmalignant).

ANATOMICAL DIAGNOSIS

Pancreatic cyst.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: I am sorry I, Arthur W. Allen is not here to tell you his operative findings. He found a large "cystic tumefaction," he called it, including the entire head of the pancreas and extending down the midline to the left. It was hard in some areas, but felt definitely cystic. I put a needle into it and withdrew 30 cc. of cloudy, thin, gray fluid. Small particles could be seen floating in the fluid, which he interpreted as flecks of calcified material. He then did another aspiration and obtained 90 cc. He thought that resection would be too great an undertaking at that time and merely did a cholecystostomy. He took a biopsy of the pancreas, on which we were able to report on chronic pancreatitis. There were large areas of lymphocytic infiltration but no evidence of tumor.

The patient went home, but came back three or four months later with a history of pain in the right upper quadrant. At that time Dr. Allen re-explored the abdomen and again aspirated the cyst, recovering over 500 cc. of thin, yellow-brown fluid. The cyst seemed fairly movable and a resection of the head and part of the body of the pancreas and surrounding duodenum was performed. A catheter was introduced into the cut end of the common duct, and this was brought through the jejunum to come out through a small jejunostomy; then a jejunocholecystostomy was performed. A gastroenteros-

tomy was done, after which a fine catheter was placed in the cut end of the pancreatic duct and the whole cut end of pancreas implanted in the jejunum below the gastroenterostomy. This catheter was brought out through the wall of the jejunum by a small jejunostomy. A third jejunostomy for feeding was placed below the others, and all three tubes were led out through a separate stab wound in the left abdominal wall. After this a cholecystostomy was done.

Here is a photograph of the cyst, which measured 12 by 9 by 7 cm. (Fig. 2). It had a thick fibrous wall with no lining epithelium that we could make out. When received, it contained about 200 cc. of

such, it has to be extensive chronic pancreatitis, destroying practically the whole pancreas, before the patient develops diabetes. I think that is nearly always correct.

DR. CASTLEMAN: We believed that the piece removed at the first operation, which showed chronic pancreatitis, may well have been due to pressure of the cyst on neighboring parenchyma. The tail of the pancreas may have had atrophic acinar tissue from the pressure on the pancreatic duct itself.

DR. COPE: But ordinarily that is not associated with atrophy of the islet-cell tissue.

DR. JONES: The number of cases observed clinically where there has been obstruction to the flow



FIGURE 2.

clotted blood. Although most of the lining was smooth, there were many irregular knob-like projections up to 0.5 cm. in diameter composed of old organized blood clot, many of which were hard and gritty and were undoubtedly the areas of calcification seen on the x-ray films.

DR. COPE: It was not malignant?

DR. CASTLEMAN: It was not malignant, and not of the papillary cystadenoma type. It was a simple cyst, the etiology of which is still unknown. I believe some would call it a pseudocyst resulting from previous areas of necrosis in the pancreas, rather than a cyst due primarily to obstruction of the duct. I do not believe a cyst would reach this size from mere obstruction to the duct.

DR. COPE: Was Dr. Allen able to visualize the tail of the pancreas? Was that fibrosed?

DR. CASTLEMAN: He did not mention it.

DR. COPE: In the cases that we have seen on the surgical service, it was rare to find such a benign localized lesion associated with a diabetic tendency and with the tail of the pancreas uninvolved. Is that your experience, Dr. Jones?

DR. JONES: I should think so. If it is chronic pancreatitis that the pathologist can recognize as

of pancreatic juice and an atrophic process that results in diabetes are extremely few.

DR. REED HARWOOD: I talked with the patient after the operation and it turned out that he had a family history of diabetes — a brother with severe diabetes. I have no way of knowing whether the pancreatic cyst brought on the diabetes or whether he had diabetes before the cyst developed.

DR. COPE: It is a mild diabetes?

DR. HARWOOD: Yes, extremely mild. At the present time he is getting 8 units of insulin, and sometimes he is sugar free.

DR. CASTLEMAN: It is now four weeks since the operation and the patient seems to be doing well.

CASE 30102

PRESENTATION OF CASE

A fifty-three-year-old Lithuanian machinist was admitted to the hospital because of cough, orthopnea and swelling of the ankles.

Except for slight dyspnea on exertion, the patient was well, and engaged in active work, until about eight weeks before entry. He then developed a

fairly severe dry cough. Three, or four days after this there was sudden onset of pain in the left side over the lower ribs. The pain was intensified by cough on deep inspiration. The patient had no fever or chills. Because of persistence of the cough, a physician referred him to a metropolitan hospital for a roentgenogram of the chest. The film was said to show "pleurisy on the left." Soon after this, pain developed in the right side that was similar to that previously suffered on the left. The patient then entered a nursing home for a stay of about a month. In the first days of this hospitalization he had no fever, but later the temperature rose to 102°F. and he was put to bed for two weeks, the diagnosis being "double pneumonia"; during that time, however, he felt well. After another week in the nursing home, when he was allowed to be out of bed, he was discharged. At that time, a week before entry, there was increase in the patient's usually slight exertional dyspnea. There was swelling of the ankles, and reappearance of persistent cough. The patient had paroxysmal difficulty in breathing at night. These symptoms progressed rapidly.

No significant past history could be obtained.

Physical examination showed a man sitting up in bed, with rapid and embarrassed respirations. The fingers were clubbed, and the nail beds "floating." The veins of the neck were engorged, and the fundi showed slight venous congestion. The feet and ankles showed pitting edema. The heart was markedly enlarged to the left, extending 12 cm. to the left of the midsternal line. There was gallop rhythm, and the sounds were of poor quality. A diastolic thrill was palpable at the apex. There were a loud apical systolic and probable diastolic murmur, a systolic murmur in the aortic area, and an early high-pitched diastolic murmur along the left sternal border in the third interspace. The pulse was Corrigan in type. Moist rales were heard over both pulmonary bases, up to the level of the spines of the scapulas. The liver edge was felt three or four fingerbreadths, and the spleen two fingerbreadths, below the costal margin. Free abdominal fluid was not evident.

The temperature was 101°F., the pulse 120, and the respirations 24. The blood pressure was 140 systolic, 40 diastolic.

Examination of the urine was negative. The blood showed a red-cell count of 4,100,000, with 10 gm. hemoglobin, and a white-cell count of 7000, with a normal differential. The nonprotein nitrogen was 23 mg. per 100 cc., the serum protein 7.3 gm. The sedimentation rate was 1.6 mm. per minute. Thirteen blood cultures were negative. The Hinton reaction was positive on four examinations; the Wassermann reaction was twice negative, and twice doubtful or unsatisfactory.

An electrocardiogram showed probable digitalis effect.

A roentgenogram of the chest showed the heart to be enlarged, particularly in the region of the left

ventricle. The aorta was not remarkable. The hilar vessels were dilated and fuzzy in outline. Both costophrenic angles were obliterated. Oblique and lateral views showed slight enlargement of the left auricle.

The patient was treated with full doses of digitalis and mercurial diuretics, and was given sedation and fluid restrictions. He lost fluid satisfactorily, and there was some clearing of the chest. The temperature, however, continued to fluctuate daily between 98 and 101°F., the pulse and respirations remaining somewhat more rapid than normal.

After three weeks in the hospital without essential progress, the patient was given massive doses of aspirin, to which there was no significant response. At about that time, occasional granular and hyaline casts and red cells began to appear in the urine. Eight weeks after admission, a course of sulfadiazine was given, a blood level of 16.7 mg. per 100 cc. being attained. The patient's temperature continued as before. There was progressive weakness, and two months after entry increasingly frequent episodes of severe nocturnal dyspnea began to occur, during which the physical signs of pulmonary edema were evident.

In the eleventh hospital week the patient expired, failing to respond to oxygen, morphine and tourniquets. There was a terminal elevation of temperature to 105°F.

DIFFERENTIAL DIAGNOSIS

DR. ARTHUR J. LINENTHAL: In the discussion of this case there are two main questions to be considered: first, the nature of the cardiac disease that led to congestive heart failure and death, and second, the nature of some other process that appeared to be present, the predominating manifestation of which was continuous fever of about four months' duration.

Regarding the heart disease, the problem is mainly one of distinguishing between the two important possibilities: rheumatic heart disease and syphilitic heart disease, either one of which might give rise to aortic regurgitation, which was the dominant, if not the only, valvular lesion present. Information concerning this differentiation may be obtained from the clinical picture, the physical examination, the x-ray examination and the laboratory findings.

The most striking features of the clinical picture were the suddenness of the onset and the rapidity of the progression of the picture of cardiac failure. This is suggestive of syphilitic heart disease, which frequently runs such a rapid course, rather than rheumatic heart disease, in which the course is almost always a chronic and prolonged one. Furthermore, at the age of fifty-three a first attack of congestive failure suggests syphilitic rather than rheumatic etiology.

Physical examination gave definite evidence of aortic regurgitation: a diastolic murmur along the left sternal margin, a Corrigan pulse and a blood pressure of 140 systolic, 40 diastolic. There was no evidence of aortic stenosis to point to rheumatic disease: there was only a systolic murmur in the aortic area, the transmission of which we do not know, there was no thrill, and there is no mention of abnormal aortic second sound.

The physical findings at the apex are difficult to evaluate. There is said to have been a "probable diastolic murmur," which could have been a transmitted murmur from the aortic area, an Austin-Flint murmur, or the murmur of mitral stenosis. There is said to have been a diastolic thrill at the apex. The exact significance of this is questionable in the absence of a definite diastolic murmur. Ordinarily this would be indicative of mitral stenosis. An apical systolic murmur can represent organic mitral regurgitation associated with rheumatic disease of the mitral valve, or can be the functional murmur of mitral regurgitation secondary to the left ventricular enlargement of aortic regurgitation. This last murmur is therefore of no differential help.

Thus the physical findings showed definite organic disease of the aortic valve, with aortic regurgitation, but in all probability no organic disease of the mitral valve. These findings are somewhat suggestive of a syphilitic etiology.

X-ray examination of the chest brought out many features. The predominant left ventricular enlargement was consistent with free aortic regurgitation. The normal aorta gave no support to the diagnosis of syphilitic heart disease, but did not rule it out. The dilated hilar vessels and the left auricular enlargement were consistent with functional mitral regurgitation, and the "slight" enlargement of the auricle, was not enough to presuppose the presence of mitral stenosis. All this evidence is in keeping with isolated aortic regurgitation due to either cause.

The laboratory data showed four positive Hinton reactions, which were good evidence of syphilitic infection. The two negative and the two unsatisfactory Wassermann reactions were in no sense against the diagnosis of syphilis, since the Hinton is the more sensitive of the two tests.

In summary, then, a fifty-three-year-old man with positive serologic tests and free aortic regurgitation developed rapidly progressive, predominantly left-sided, cardiac failure, a picture more consistent with syphilitic than with rheumatic disease of the aortic valve.

The picture of congestive heart failure, both of the left and of the right side of the heart, was quite clear. The onset was rather sudden, with increasing exertional dyspnea, ankle edema, cough and paroxysmal nocturnal dyspnea. Examination revealed pitting edema, cardiac enlargement, gallop rhythm,

poor heart sounds, orthopnea, rales in the lungs, and engorged neck veins. The negative urine and normal nonprotein nitrogen suggest that the amount of congestion in the kidneys was slight if any.

On cardiac therapy he did well at first, losing fluid satisfactorily. Apparently the paroxysmal dyspnea also improved, for we are told that it reappeared toward the end of his hospital stay, when he died in uncontrollable pulmonary edema. We do not know whether there was any reappearance of the right-sided cardiac failure.

In addition to these findings, however, there were others less easily explained on the basis of cardiac failure. The liver was large, but we are not told whether it was tender or whether it subsequently decreased in size with diuresis. With hepatic enlargement due to congestion of such sudden onset and short duration, one would expect that the liver would have been quite tender and painful. Palpable splenic enlargement, two fingerbreadths below the costal margin, is unusual with failure of such short duration, being usually seen in long-standing cases of chronic passive congestion, often with cardiac cirrhosis of the liver.

There remain other findings that cannot be explained on the basis of heart failure. The continuous fever was apparently the most striking feature of this patient's illness. It started three or four weeks before the onset of the failure and persisted even after the cardiac failure had improved. The elevated sedimentation rate was probably an accompaniment of the fever. The clubbed fingers could fit in with several of the disease pictures to be mentioned below, or they could represent a congenital and an entirely unrelated phenomenon. There was a moderate hypochromic anemia, which is also unexplained.

As the first possibility to explain these findings, one thinks of pulmonary disease. The patient's illness before the onset of cardiac decompensation involved the lungs. It started with cough and was followed by pleuritic pain, first on one side and then on the other. A film at that time is said to have shown "pleurisy on the left," but the meaning of this is not clear. Subsequently the patient developed fever, and although he had no symptoms, he was put to bed and was said to have had "double pneumonia." Following closely on this period of bed rest, he developed the picture of cardiac failure. Apparently the cough that marked the onset of the whole illness subsided, only to reappear with the onset of failure and to persist for an indefinite time.

One thinks of bilateral pulmonary infarctions with emboli arising from silent peripheral phlebotrombosis, although there is no story of hemoptysis. Low-grade pulmonary infection may arise on the basis of previous infarction. Against this idea, however, as against any attempt to explain the fever on the basis of pulmonary disease, is the demonstration of normal lungs by x-ray. Except for

the hilar congestion and minimal fluid in the costophrenic angles, there was no evidence of parenchymal disease. This finding is strong evidence against pulmonary infection, bacterial or otherwise, against pulmonary malignancy and against pulmonary infarction, at least at the time the film was taken.

It is difficult to explain the nature of the pulmonary episode at the outset. It appears to have been a low-grade, rapidly subsiding pulmonary infection.

Other possibilities considered by those in charge of the patient included subacute bacterial endocarditis. Consistent with this diagnosis are the fever, the clubbed fingers, the anemia, the enlarged spleen, and the normal white count in a patient with known cardiac disease. Against it, however, are the thirteen negative blood cultures, the absence of any clear-cut embolic phenomena, and the rarity of this complication with syphilitic heart disease, which we assume this patient had.

Although the picture was not that of active rheumatic fever in an adult, this disease was considered, and salicylates were tried. There was no response. It is interesting to note that the casts and the red cells that appeared in the urine at that time may well have been due to the effect of the massive doses of aspirin on the kidneys.

Finally the patient was given sulfadiazine, presumably on the chance that he might have had some bacterial infection susceptible to this drug. Again there was no response.

We are forced then to look elsewhere for the cause of the fever, and returning to those findings probably unexplained by the congestive failure, we have enlargement of the liver and of the spleen. Together these suggest hepatic cirrhosis, and in a known syphilitic patient one thinks of syphilitic involvement of the liver. This disease is usually asymptomatic and is sometimes accompanied by fever, as is cirrhosis of other types. Cirrhosis can give rise to clubbed fingers, and the anemia, although not of the usual macrocytic type, is not inconsistent.

Finally, a malignant neoplasm must be considered in any unexplained febrile illness in a person of this age. No primary site was apparent, but metastatic cancer of the liver is possible, although this would not explain the splenomegaly. Possibly the splenomegaly was entirely unrelated, having been the sequela of some such disease as malaria in earlier life.

One would like to be able to explain the whole picture by one disease process, and this can be done by supposing that this patient with syphilitic heart disease also had syphilitic disease of the liver.

CLINICAL DIAGNOSES

Acute rheumatic fever.

Rheumatic heart disease, with aortic regurgitation.

Congestive heart failure.

DR. LINENTHAL'S DIAGNOSES

Syphilitic heart disease, with aortic regurgitation.
Congestive heart failure.

Cirrhosis of liver (? syphilitic).

ANATOMICAL DIAGNOSES

Endocarditis, subacute bacterial, of aortic valve (pneumococcus Type 13).

Congenital bicuspid aortic valve.

Cardiac hypertrophy.

Embolic nephritis.

Splenomegaly.

Peripheral edema.

Pulmonary edema and congestion.

Bronchopneumonia.

Central congestion and necrosis of liver.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The clinician in charge of this patient tried to establish a diagnosis of bacterial endocarditis and, like Dr. Linenthal, finally voted against it. The autopsy, however, shows a subacute bacterial endocarditis involving the aortic valve. The valve had been previously damaged, but by neither a rheumatic nor a syphilitic process. The valve was a congenital bicuspid and on each cusp were attached friable vegetations 6 to 8 mm. in diameter. Some of these were nodular and contained foci of calcification. There was perforation 8 mm. in diameter through the anterior cusp, which accounts for the regurgitation. We were able to recover Type 13 pneumococci from the heart's blood and the vegetations. The mitral valve was negative. The heart was moderately hypertrophied, weighing 500 gm.

As evidence of heart failure, we found peripheral edema, pulmonary edema and congestion, and central congestion and necrosis of the liver. The spleen was enlarged, weighing 500 gm. There was also terminal pneumonia in the left upper lobe.

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THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

RED CROSS BLOOD-DONOR SERVICE

A CERTAIN degree of confusion has continued to exist regarding the exact role of the Red Cross blood-donor centers, their functions and obligations and their relation to civilian defense, hospital blood banks and the private citizen. Many of the last, indeed, even including Red Cross workers, entertain the belief that the blood-donor center is a sort of civic pool to be drawn on in case of emergency, as one might take a book from a public library, were one bookishly inclined.

In view of the enormous quota of blood that the Red Cross has committed itself to obtain for this year of warfare, — a quota that, as previously in-

dicated,* is not yet being met, — a statement has been issued by Mr. Joseph R. Hamlen, chairman of the Boston Metropolitan Chapter, to remedy the confusion and ensure the continuance of good public relations.

The most important point to be made clear is that the American Red Cross is collecting blood exclusively for the armed forces at the request of the United States Army and Navy. As Mr. Hamlen states:

The blood at no time belongs to the Red Cross, but rather, from the moment it leaves the donor's veins, it is the property of the United States Army and Navy. The Red Cross is specifically forbidden from diverting the blood, except under direct orders of the Army and Navy. Under certain rare circumstances, such as the Cocoanut Grove disaster or enemy bombing, this blood can be released, but only with the consent of the Army and Navy.

The Red Cross is further under obligations not to furnish the names of donors to persons seeking donors for private patients, not to conduct any sort of a campaign to enlist donors for private patients, and to accept no blood other than that taken at its own blood-donor centers or by mobile units of those centers. Moreover, by an agreement between the American Red Cross and the Office of Civilian Defense, all hospitals whose blood banks are financed by OCD funds must refrain from public appeals for donors through the newspapers, radio or other accepted mediums of publicity within seventy-five miles of a Red Cross blood-donor center. The Red Cross Blood-Donor Service thus receives the priority it must have to attain its quotas — a service of paramount importance to a nation at war.

The private citizen may still be supplied with blood to the utmost limit of his needs, but it must be obtained at hospitals with blood banks, or from private or professional blood donors. For Army and Navy needs, which constitute the number one priority today, the Red Cross must have a clear track and the co-operation of every patriotic citizen.

EPIDEMIC JAUNDICE

Two types of cases of jaundice have been encountered during the present war, both of which may be said to have occurred in epidemic form. Catarrhal jaundice, or what the British like to call

*Editorial. Share the blood, *New Eng. J. Med.* 230 121, 1944.

"infective hepatitis," has probably occurred among the armed forces in this country, but its incidence has not been excessive and no serious or extensive epidemics of this disease have been reported. This disease, however, has occurred in epidemic form among civilians in England,^{1, 2} among the British armies in the Middle East³⁻⁵ and among German troops in occupied territories,⁶⁻⁸ and it is probably quite widespread in other localities. The second form of jaundice, which has occurred both in the American and British armed forces and in Brazil has come to be known as "homologous serum jaundice"⁹ and has already been commented on in these columns.¹⁰ The most widespread occurrence of this form of jaundice has been after vaccination against yellow fever. All the vaccines responsible for this type of jaundice have contained attenuated yellow-fever virus and human serum. Vaccines using the same strain of virus but omitting the human serum have now been used for more than a year, and so far as is known, no cases of jaundice have resulted.

The clinical features of the two types of jaundice are sufficiently similar so that it is difficult to tell them apart. Most cases of post-vaccination jaundice, however, have had a severer course, and fatalities have been commoner in this form. Deaths from either type of jaundice have been associated with widespread liver damage — that is, they have been due to acute or subacute yellow atrophy.

The chief distinction between the two forms of jaundice has been on epidemiologic grounds. The incubation period of catarrhal jaundice, according to data available in cases occurring after single or short exposures, is about four weeks but ranges from twenty to forty days. Patients with the disease are infectious during the preicteric stage and for a few days after the jaundice appears. Although no virus has been isolated from cases of catarrhal jaundice, the disease is believed to be transmitted from patient to patient by droplet infection, and suggestive results of experimental nasopharyngeal transmission have been reported.¹¹

Homologous serum jaundice, as implied in the term, has occurred only after the inoculation of convalescent serums or of vaccines containing human serum. The incubation period is two to four months, shorter incubation periods being quite rare.

Infections acquired from simple exposure to cases of post-immunization jaundice are extremely unusual. When they do occur, however, they are helpful in understanding the nature of this disease. In such cases, which occurred in uninoculated persons following contact with patients who developed jaundice after receiving measles convalescent serum, have been reported.¹²

Several explanations for homologous serum jaundice may be mentioned. Is the jaundice following yellow-fever immunization a mild form of yellow fever in which the attenuated virus has retained viscerotropic properties? This seems unlikely because of the fact that no jaundice occurs with the same virus when human serum is not incorporated in the vaccine. Furthermore, this fails to explain the cases occurring after convalescent serums given for other diseases and which have similar clinical features, as well as a long incubation period. A second possibility is that the infected serum contains a virus that is capable of producing hepatitis in the homologous species. In this connection the virus may be the same as that of catarrhal jaundice but modified by the treatment to which it has been subjected in the preparation of the vaccine or of serum. Furthermore, the type of bodily reaction may be changed because of the fact that the infection is acquired after subcutaneous inoculation rather than by the nasopharyngeal route, which is the natural one for catarrhal jaundice. This might account for the long incubation period of homologous serum jaundice. Another possible explanation for this form of jaundice depends on the supposition that some toxic agent is introduced in the process of preparing the immunizing material. Finally, one might suppose that the homologous serum has been altered in the process of preparation in such a way that it becomes antigenic and capable of producing antibodies that react specifically with newly manufactured proteins in the liver, thus causing an inflammatory antigen-antibody reaction. The two explanations are difficult to rule out or to prefer.

Some recent experiments in transmission support the view that the virus is identical with that of catarrhal jaundice or similar to it. Findlay and Martin¹³ obtained nasal washings from three patients in the preicteric or early icteric stage of jaundice.

e following yellow-fever vaccination and included these washings into the nares of three healthy unteers. The latter came down with jaundice er incubation periods of twenty-eight, thirty, and y days. There was considerable variation in the erity of the illnesses of these recipients, but e symptoms were similar to those of infective patitis.

A second series of experiments designed to determine the properties of any virus agent that might responsible for the jaundice following yellow-er immunization were carried out by workers at e National Institute of Health.¹⁴ They produced ndice in human beings by the inoculation of two fferent lots of yellow-fever vaccine containing oled human serum. They also produced jaundice inoculating small amounts of filtered serum from hef an individual or a group who had previously ceived yellow-fever vaccine containing human rum and who subsequently developed jaundice. ey concluded that the jaundice-producing agent filterable and survives drying in a vacuum, storing r long periods in serum at 4°C. and heating at °C. for half an hour in the dried state. They also tained evidence that this agent is present in the ood before the jaundice appears but not two and a lf months after the disappearance of the jaundice. heir experiments indicated that the agent is stroyed by ultraviolet radiation.

These two groups of experiments support the view at the cause of homologous serum jaundice is a rus similar to, if not identical with, that of ordi-ary catarrhal jaundice. If this view is correct, the revention of such jaundice depends on exercising rther care in the selection of donors for human rum or plasma: one must avoid those who have ad or may have had catarrhal jaundice within two r three months of the time when they are bled.

A recent editorial calls attention to a possible ource of epidemics of catarrhal jaundice.¹⁵ This is ased on a report by Hallgren of an explosive in-stitutional outbreak in which the infective agent was robably carried by water, inasmuch as a leak in the ain sewer system might well have accounted for he pollution. Such a finding appears to be sig-ificant in the prevention and control of epidemic nfectious hepatitis.

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MEDICAL EPONYM

WATERHOUSE-FRIDERICHSEN SYNDROME

Rupert Waterhouse (b. 1873), pathologist and assistant physician at the Royal United Hospital, Bath, reported "A Case of Suprarenal Apoplexy" in the *Lancet* (1:577, 1911). A portion of the article follows:

A male child, aged 8 months . . . throughout the morning had been very drowsy and had "looked strange" . . . had not seemed in pain, had taken nourishment readily, and . . . the bowels had acted as usual. About 3 o'clock in the afternoon he vomited. . . . Previously the child had always seemed perfectly healthy. . . . On account of the parents' conscientious objection the child had never been vaccinated. . . .

On admission the infant was obviously very ill: complexion grey, eyes dull, breathing rapid, shallow, and noiseless; temperature 100.4°F., pulse 140, and respirations 72. Rales could be heard all over the chest. . . . There were no signs of meningitis, and nothing abnormal was to be seen in the mouth or fauces. Two hours after admission an extensive eruption of purple spots and blotches appeared over the whole trunk, upper arms and thighs. . . . The child rapidly grew worse, . . . and death occurred at 7:30 p.m.

. . . . The post-mortem examination was made 22 hours later. . . .

The lungs were congested and oedematous. . . . The suprarenal capsules were striking objects even before their removal from the body; of little more than normal size for a child of this age, they were both of a deep purple colour and evidently the seat of haemorrhage. . . . Microscopically the structure of the medulla was seen to be completely destroyed and replaced by effused blood. . . . All the other organs appeared natural. . . .

The case related above appears to form one of a distinct group . . . all infants between the ages of 2 and 15 months, and all of whom died after an illness lasting in the majority less than 24, and in none more than about 48 hours. In all but three a haemorrhagic rash of greater or less extent was present. . . . Apart from the lesions of the adrenals and the haemorrhagic rash, the most constant post-mortem findings have been intense engorgement of the lungs. . . .

Eight years later Carl Friderichsen (b. 1886), then assistant in the children's department of the

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DEATHS

DORE — The Rev. Francis J. Dore, for the past nineteen years head of the biology department at Boston College, died February 28. He was in his sixty-eighth year.

Fr. Dore was graduated from Boston College in 1898, and from the Harvard Medical School in 1902. He practiced medicine in Boston until he entered the Society of Jesus in 1907. He was regent of the school of pharmacy at Fordham University from 1918 to 1922, and in 1925 came to Boston College from St. Andrews-on-the-Hudson, Poughkeepsie, New York. He was an honorary fellow of the Massachusetts Medical Society.

Two brothers and two sisters survive.

POTE — Leonard H. Pote, M.D., of Somerville, died December 3, 1943. He was in his seventieth year.

Dr. Pote received his degree from Harvard Medical School in 1900. He was a member of the Massachusetts Medical Society and the American Medical Association.

CORRESPONDENCE

CONFUSION OF NAMES

To the Editor: Since the similarity of my name and office address with those of another who is licensed to practice medicine in Massachusetts has, in the past, caused much confusion, I respectfully request that physicians who see fit to refer patients to me give my full name and exact office address.

184 Bay State Road
Boston

JOSEPH RESNIK, M.D.

AGE LIMIT RAISED FOR RESTRICTED SHORE DUTY IN MEDICAL CORPS OF THE NAVY

To the Editor: On March 1, owing to the continuing urgent need for physicians in the Navy, the maximum age limit for specialist medical officers was raised from the age of fifty to fifty-five. This office will therefore be glad to accept applications from physicians who have not reached their fifty-fifth birthday.

The following is quoted from the telegram of authorization:

Authority is hereby granted to forward applications for appointment in class MC-V(S) of individuals whose physical qualifications justify their appointment for limited shore duty only. If approved it is intended to appoint these officers to duty in naval dispensaries, navy yards, naval training stations, and to the Navy and Marine Corps recruiting service, thus making available for sea and foreign assignments physically and otherwise qualified medical officers now detailed to this type of duty.

COMMANDER JOHN P. MONKS, MC-V(S) U.S.N.R. Senior Medical Officer
Office of Naval Officer Procurement
150 Causeway Street
Boston

NOTICES

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis

Association, 554 Columbus Avenue, Boston, on Tuesday, March 21, at twelve noon. Dr. Chester S. Keefer will on the topic "Penicillin."

Physicians are cordially invited to attend.

TUFTS MEDICAL ALUMNI ASSOCIATION

The annual meeting and dinner of the Tufts Medical Alumni Association will be held on March 29 at the Plaza Hotel, Boston. The committee on arrangements consists of Dr. William E. Browne, chairman, Dr. Harry Blum, secretary-treasurer, and Drs. Carl Bearse, Roy J. Heff, James W. Manary and Frank R. Ober.

The guest speaker will be Dr. Morris Fishbein, editor of the *Journal of the American Medical Association*, who will on the subject "Probable Changes in the Practice of Medicine, Harmful to the Patient, If Bills Now Pending in Washington Become Law." Dr. Leonard Carmichael, president of Tufts College, will speak on the topic "First Fifty Years as a Prelude to Greater Things." Other speakers will include Dr. A. K. Paine, president of the American Medical Association, Captain A. Warren Stearns (MC), U.S.N.R., on leave, and Dr. Carl T. Phillips, of Putnam, Connecticut.

NEW ENGLAND PATHOLOGICAL SOCIETY

The next meeting of the New England Pathological Society will be held in the amphitheater of the Children's Hospital, Boston, on Thursday, March 16, at 8 p.m.

PROGRAM

Peripheral Thrombosis and Gangrene of the Extremities in Early Life. Dr. Robert E. Gross.

Neurofibroma with Special Reference to Skeletal Involvement. Dr. William T. Green.

Tumors of the Brain and Spinal Cord in Infancy and Childhood. Dr. Francis D. Ingraham.

Some Peculiarities of Malignant Tumors in Early Life. Dr. Sidney Farber.

Physicians and medical students are cordially invited to attend.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

The 358th meeting of the New England Ophthalmological Society will be held at the Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, on Tuesday, March 16, at 8 p.m.

Following the business meeting, Dr. David G. Coggeshall will speak on the topic "Some Disturbances of Eye Movement in Cerebellar Disease." Dr. Joseph Igersheimer will speak on the subject "Intraocular Pressure and Its Relation to Retinal Extravasation."

ALLERTON HOSPITAL

The regular monthly meeting of the Medical Staff of Allerton Hospital will be held at the Nurses' Home, 350 Brookline Street, Brookline, on Thursday, March 16, at noon. Luncheon will be served.

SOCIETY MEETINGS AND CONFERENCES CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 16

THURSDAY, MARCH 16
*9.00-10.00 a.m. Medical clinic. Dr. S. J. Thannhauser. J. Pratt Diagnostic Hospital.
†5.00 p.m. Minimal Water Requirements of Castaways. E. Gamble. Amphitheater, Children's Hospital, Boston.
*8.00 p.m. New England Pathological Society. Amphitheater, Children's Hospital, Boston.

FRIDAY, MARCH 17
*9.00-10.00 a.m. Brain Electricity: Observations on the Cephalogram. Lieutenant Commander Herbert J. Harlow, U.S.N.R. Joseph H. Pratt Diagnostic Hospital.
(Continued on page xiii)

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Number 11

THE NUTRITIONAL SITUATION IN THE CAMPS OF THE UNOCCUPIED ZONE OF FRANCE IN 1941 AND 1942 AND ITS CONSEQUENCES*

RENÉ ZIMMER, JOSEPH WEILL AND MAURICE DUBOIS

NIMES, FRANCE

EARLY in 1942 the Commission on Hygiene called attention to a grave danger threatening the very existence of the internment camps. Malnutrition, or the so-called "disease of starvation," had invaded them. Although its initial attack in the spring of 1941 was halted by the coming of summer, a new wave swept over the camps with the first arrival of cold weather. The disease spread rapidly, like a contagion, revealing profound physical exhaustion and extreme misery. The symptoms, slight at first, then more and more marked, became increasingly serious and showed in many respects the classic picture observed during famines, whereas other, much less well-known symptoms seemed peculiar to this particular outbreak of malnutrition. The number of deaths increased. During the first period, from September, 1941, to January, 1942, there was a daily average of 2 deaths in each camp, and in certain camps 5 every two days. Four weeks after a group of 40 patients had been transferred to a camp hospital, they were all dead.

This disease resembled an epidemic, spreading to all the barracks, penetrating into all the divisions, striking all the camps, and threatening a population of more than 10,000 men, women and adolescents. The men were affected first and seemed to be much less resistant than were the women and the young people, but later the character of this collective disease underwent profound changes.

The commission sounded the alarm at the meeting of January 14, 1942. It proposed urgent measures of assistance, and at the same time submitted them to the approval of the inspector general of the camps. The plans included the following essential features: the assignment by the commission of

physician-investigators to the camps, their mission being to examine all the internees from the point of view of nutrition and to organize and co-ordinate a program of assistance by all the relief agencies in collaboration with the sanitary services of the camps; hospital care for those suffering from the disease of starvation, in barracks especially fitted out to facilitate their observation and treatment; organization of special dietary kitchens under the common responsibility of the relief agencies; provision of urgent medical treatment where it was needed, together with the administration on a large scale of dietary products, vitamins, minerals and general stimulants; and isolation of those in danger of developing serious starvation symptoms in prophylactic centers separate from the camps proper.

Today we report the first results of this program of assistance and observation. First of all we wish to express our thanks to the inspector general of the camps, by whose swift and energetic administrative measures the organization of assistance was made almost immediately possible.

The medical investigators began their work in most of the centers in February, 1942. Kitchens were organized for the cachectic (starving) patients in the most important camps. A close collaboration was established between the medical investigators and the sanitary services of the camps. Nine thousand persons have been thoroughly examined and regularly followed up.

The plan of the physicians assigned by the Commission on Hygiene included an investigation in the huts of patients affected by the syndrome of starvation, a clinical and therapeutic study of the cachectic patients under hospital care in the barracks, a study of the nutritional situation, the co-ordination of the different relief agencies in the camps and the elaboration of medical principles guiding their work and a critical study of the results obtained.

PRELIMINARY DATA

The investigation took the form of a methodical medical examination of all the inhabitants, section

*This report was originally presented on July 1, 1942, by the Commission on Hygiene of the Co-ordinating Committee for Relief in the Camps at Nimes, France. The commission consisted of the representatives of the organizations interested in the camps, namely, the Unitarian Service Committee, the Swiss Red Cross, and the Jewish (various) attempts then being made to solve the medical and hygienic problems arising in the supervised concentration camps in France, to collaborate for the sanitary protection of the internees and to establish contact with the international organizations interested in these problems. The report was translated and shortened under the auspices of the Unitarian Service Committee.

by section and barrack by barrack. Of all the internees of the camps 85 to 95 per cent were thus examined. At a preliminary session they were weighed and measured, undressed. Their medical histories were noted, their pulse rates and arterial blood pressures were recorded, and whenever possible their weights before internment were ascertained. At a later session the patients were medically examined, undressed, and the findings were entered on individual record cards. The investi-

gation had to be restricted to simple and rapid examinations, as is necessary in the study of large groups.

The following criteria were used for the primary classification of the patients: height and weight, condition of the skin and the adjacent subcutaneous tissues, muscular tonus, posture, condition of the cardiovascular system, the presence and location of edema and the blood picture. Such criteria were sufficient to permit classification of the patient with regard to the urgency for and importance of the treatment required by their condition.

Criteria

Measurements of height and weight. A weight-height index of all the examined persons was set up, making it possible to judge at a glance the weight conditions of the internees. The index has a practical value only if it is calculated in relation to the physiologic coefficient of weight to height, deter-

mined according to the corrected tables of Dubois-Reymond. The results of such measurements on the men and women of an entire camp are presented in Figures 1 and 2, plotted as frequency of occurrence against percentage of physiologic weight and against a weight-height index. It was necessary to take into consideration, in weighing and measuring, the errors in weight caused by the edemas and those in height caused by the frequent scolioses due to the osteopathy of starvation. It was therefore important

to register whenever possible the preinternment weight and height as entered on the military identification papers of the men.

Although a considerable loss of weight in a given subject is a factor of definite prognostic value nevertheless experience has shown that it does not allow one to pronounce his condition as irreversible. Regular weighing has more significance if it is done simultaneously for a whole camp and if the results among the cachectic patients are compared with the weight of noncachectic persons in the same camp.

It has been observed that considerably emaciated patients almost always develop hernia and that this symptom is hardly ever absent even in young men who are precachectic subjects.

Examination of skin and subcutaneous tissues. From the threatened to the cachectic stage, the atrophy progresses through all degrees, arriving finally at a stage of veritable "anatomical dissection." The degree of atrophy may best be estimated by examin-

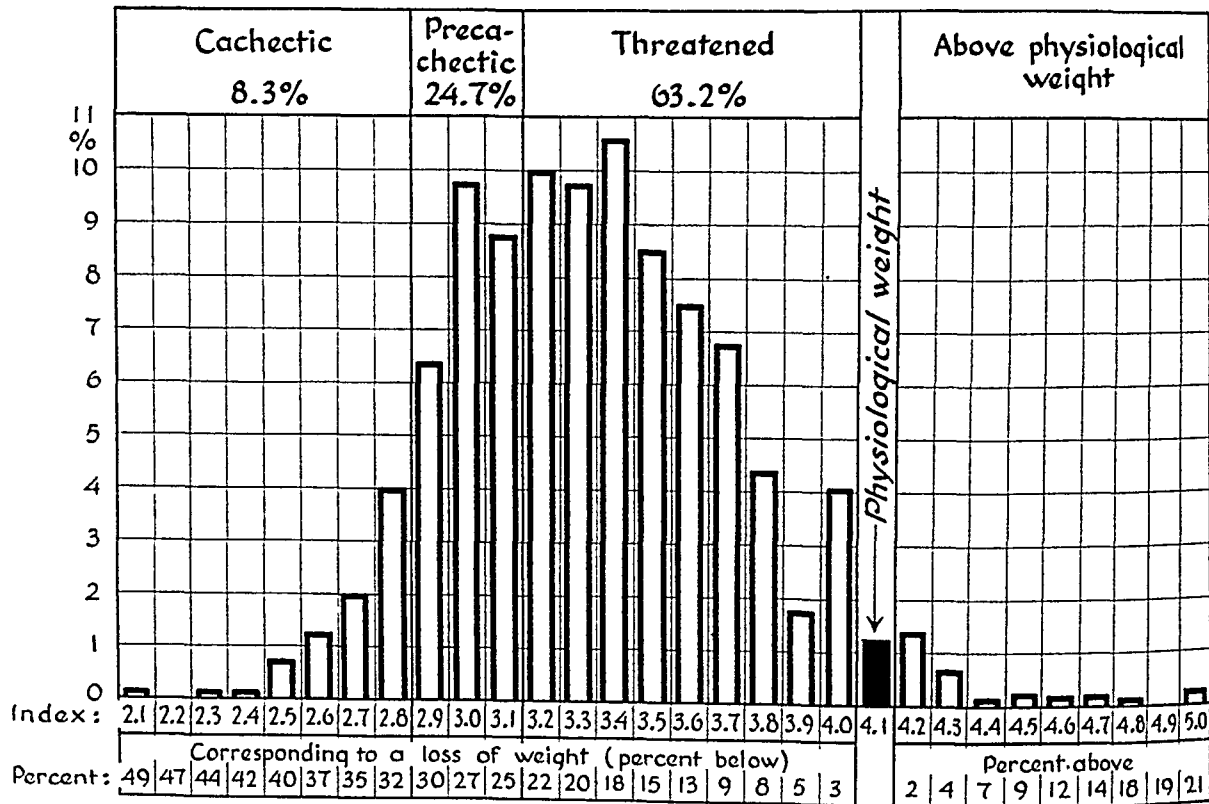


FIGURE 1. Percentage Distribution of Male Inmates of Huts A, D, E, F, G and H. According to a Weight-Height Index (Camp Gurs: June, 1942).

ing the patient posteriorly. In the final stage, particularly in the case of formerly obese persons, the skin hangs on the body like a garment that has become too large.

Muscular tonus. The signs of muscular hypotony could be observed quite early in a large number of cases. This explains to a certain degree the difficulty that many patients had in standing up. In several photographs it was noticed that the subject was unable to keep his head motionless. The posture of the patients was defective. Scoliosis occurred with increasing frequency. At a certain stage the patients dropped the things they held in their hands. They became unable to make the slightest muscular effort. Measurements made with the dynamometer

signal of the state of starvation. It was accompanied by the classic sign of empty peripheral veins.

Circulatory apparatus. Systematic registration of the pulse — rate, quality and rhythm — is important partly on account of the ease by which these measurements can be taken and partly for the valuable information that they furnish. Sometimes acceleration of the pulse, or tachycardia, was observed, sometimes a slowing, or bradycardia. At a certain stage there was sometimes irregularity of the pulse rate. The arterial blood pressure was measured in all the patients.

Edema. The edema was most significant if it was fixed, large and visceral. A characteristic physiognomy of the undernourished caused by a combina-

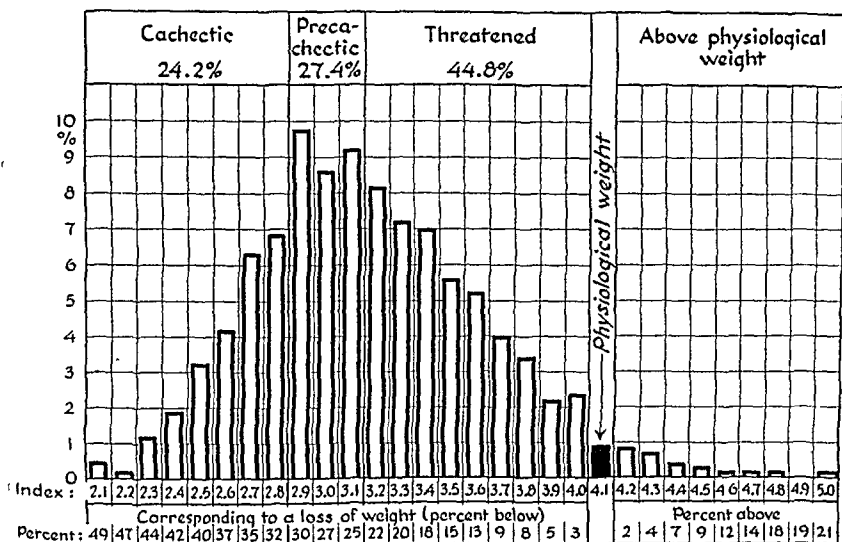


FIGURE 2. Percentage Distribution of Female Inmates of Huts I, J, K, and L. According to a Weight-Height Index (Camp Gurs; June, 1942).

showed that in a number of patients the figures obtained were smaller than those that would correspond to the strength of a small boy of ten or twelve.

Position. In the advanced stage the patients were unable to stand up, and were obliged to creep on all fours to get back to their beds. It was often of interest to measure the length of time during which the patients were able to stand. After a few seconds or minutes on their feet they complained of pricking pain in the limbs and of trembling, sometimes accompanied by profuse sweating. Fainting was frequent when attempts were made to maintain a standing position and often constituted the alarm

tion of swellings due to edema and anemia was the sign of decided physiologic disturbance.

Blood examination. Examination of blood taken at random from the undernourished showed in every case the presence of anemia.

Classification of Patients

As in the presence of a large epidemic of disease, it was important to isolate from the beginning those who were seriously affected, and furthermore to discover the first symptoms of malnutrition in others in order to limit the damage by energetic prophylactic measures. The fact that the patients exhibiting the syndrome of malnutrition were concentrated

in one place and subject to a uniform, easily controlled discipline made possible an extensive scientific analysis of the symptoms observed as well as observation of the development of the application and the study of an appropriate diet. This study may enable us to oppose effectively this syndrome, which is beginning to make its appearance among the general French population.

After examination each internee was classified under one of the following categories: cachectic, precachectic, threatened and normal.

The cachectics were immediately recognized from a distance by their extreme emaciation and their characteristic physiognomy. Their skeletonlike thin-

patients (3.7 per cent), 839 precachectic patients (9.3 per cent) and 4000 threatened persons (42.6 per cent), the remainder (42.6 per cent) appeared not being in need of immediate medical attention.

Malnutrition, which imitates some of the characteristics of a virulent epidemic of communicable disease, had not yet reached its peak in the camp. Systematic investigation revealed each week precachectic patients and those threatened with this condition.

CLINICAL AND THERAPEUTIC STUDY

According to the results of the preliminary investigation, it appeared that half the actual population

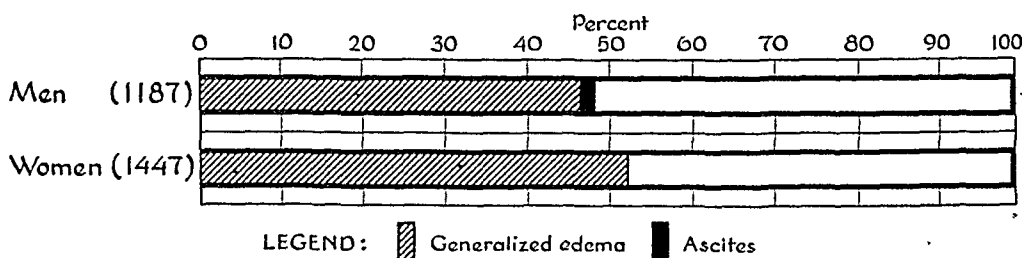


FIGURE 3. Incidence of Edema of Starvation among Men and Women, Expressed as Percentage of Total Inmates (Camp Gurs: June, 1942).

ness was impressive; muscular and skin atrophy was general. The subcutaneous layer of fat had disappeared a long time previously. The skin was dry and scaly. Many adults of average height were no more than 40 kilograms in weight. The complexion of these patients was either ash gray or of a subicteric pallor, depending on the predominance either of a shade of cyanosis or of a hemolytic process, but the pallor of the mucous membranes and the anemia were features of almost all cases. Combined with their emaciated features the patients presented a corpse-like appearance. The detailed clinical description of this type of patient is given below.

The precachectic patients showed the same symptoms to a lesser degree. Both muscular atrophy and anemia were less pronounced. The loss of weight was not so far advanced and the general state was less serious. The application of different tests showed that they had been affected less seriously.

The threatened patients had on the whole maintained a better general state of health than had those in the previous two categories. Here the tendency toward the edemas of starvation had begun to appear, but they were transitory, shifting and recurrent. Emaciation was, however, quite common. In this group were included the convalescents from typhoid fever and patients with acute gastric and duodenal ulcers, advanced tuberculosis and Parkinson's disease, as well as those with chronic decompensated heart disease.

In a population of 11,000 internees, of whom 9000 were examined,* there were found 331 cachectic

*It is not clear from the text of the report whether the 2000 subjects not examined were considered normal and free from medical need or whether the 3830 subjects not included among the three categories in the 9000 examined were normal. — TRANSLATOR.

of the camps was threatened by the form: symptoms of the disease of starvation, which appeared in various clinical forms.

Clinical Forms of Starvation

Wet form. Approximately 50 per cent of the internees who were examined showed the edema of malnutrition. It was found especially among Spaniards and Italians. Edema was not, however, the sole or pathognomonic symptom of this functional disturbance.

Contrary to the usually accepted ideas about our initial observations, we found a higher proportion of edemas of starvation among women than among men. Still, a greater number of men showed bradycardia and lowered blood pressure, which proves that they had been more seriously affected. Also it was especially among men that ascites occurred with relative frequency (Fig. 3). In accordance with what has often been stated, we found that edema affected young girls between the ages of seventeen and twenty-two who had fairly regular menses.

These edemas were located similarly in the same considerable proportion of the patients, in the same parts of the body as follows: the top of the feet, the malleolus on the inner side of the ankles, the lower part of the face, under the chin, that over the cheekbone, and the eyelids.

The soft, white edema, at first transitory, became gradually fixed after several relapses. This was observed especially in the lower extremities. A certain number of cases of edema were observed in which the patients were un-

of its existence or were not uncomfortable because of its presence. Ascites formed about 10 per cent of the edemas, and was more resistant to treatment with diuretics and additional feeding than was peripheral or subcutaneous edema.

Sometimes edema was observed in men showing a generally satisfactory state of health with no emaciation or other symptoms of malnutrition, with well-developed muscles, and with the subcutaneous layer of fat preserved. Almost all these men belonged to the canteen or kitchen staffs. This edema was caused by unbalanced diet or was of toxic alimentary origin.*

Certain associated symptoms occurred in all clinical forms of starvation. In addition to edema, the patients suffered from frequent urination, especially at night. This symptom was related either to the general demineralization or to the cold, because the nights were cool and the barracks drafty.† Pleural effusion, another form of visceral edema, was of more frequent appearance. It differed neither in development nor in prognosis from other forms of edema.

On the whole, the patients with edema maintained good appetites until a very advanced stage of their illness. The extreme fatigability from which they all suffered led, at a certain stage of the disease, to a persistent painful sensation. Sometimes the pain appeared only after a slight effort. Then the typical physiognomy of the starving cachectic patient appeared — the anemic and puffy features — and marked emaciation. Infection of the skin was frequent, and great sensitiveness to cold developed. The body temperature was often low, sometimes below 35°C. (95°F.).

Examination of blood taken at random from cachectic patients and those threatened with this condition showed that all were anemic. In none of the specimens examined did the red-cell count reach 4,000,000. In the great majority it was approximately 3,000,000. In hardly 5 per cent of all cases was the hemoglobin above 70 per cent. In all other cases it ranged about 60 per cent.

As regards both blood values and weight, the danger point was found to be a diminution of 30 per cent from the physiologic norm.

Urinalysis did not show pathologic features.

Dry form. The dry form was characterized by the absence of edema. It was found especially among the Spaniards and Italians — a reason for its pre-dominance, for example, in the camp at Rivesaltes. It should be mentioned that these men had been suffering from chronic undernourishment for many years, and their ancestors for centuries. Their skin was dry, atrophied and often scaly, and the atrophy in these cases took particularly severe forms.

*Or possibly from vascular stasis related to long hours on their feet — TRANSLATOR.

†Perhaps the bladder wall lacked tone or there was infection of the urinary tract. — TRANSLATOR.

Anemic form. Examinations of the blood smears now under way show a certain number of hyperchromic anemias — 43 per cent of the cases studied. This finding, combined with the results of neurologic examinations, is of great pathological and therapeutic importance. It would be worth determining whether the lack of the extrinsic principle, present especially in meat, is responsible for anemias of the pernicious type, combined sometimes with the neuroanemic syndrome. It is to be noted that the patient showing the most refractory neurologic symptoms, in spite of having gained in weight, was one whose blood analysis gave a color index of 1.23, with 57 per cent hemoglobin, 2,330,000 red corpuscles and 2700 leukocytes. The sedimentation rate of these patients was not as a rule accelerated.

Petechiae with segmental distribution were observed in some cases on the dorsum of the hands and forearms.

Vasolabile form. At the beginning of the illness the blood pressure and disturbances of the circulatory system were irregular. They showed deviations from the normal in both directions, sometimes between morning and evening, especially in the case of patients less severely affected. Later hypotension became constant; it was usually combined with bradycardia, which, transitory at first, also became permanent. At that point hypotension became an indication of the gravity of malnutrition. Hypertension, which was observed more frequently than is generally supposed, in spite of the general asthenia and loss of strength that occurred in severe cases, remained permanent up to the terminal stages.

The heart, like the other muscles, seemed to suffer from hydermia and atrophy. One was frequently surprised to find a double first sound without any other sign of tachycardia. Irregularities of rhythm — partial or complete arrhythmia — were not observed oftener than under other conditions.

Neurologic form. Ataxia and Romberg's sign were the most noticeable symptoms of the neurologic form. The reflexes were as a rule exaggerated. Polyneuritic pains and paresthesias were present. Examination of the ears was usually negative. General sensitivity was normal. The rate of blood sedimentation was generally much accelerated. Some patients showed a striking mixture of the Parkinsonian and ataxic syndromes. The muscles became spastic and the movements of the hands jerky, and the feet described random semicircles on walking. Once the patients had started on their way they had a fixed posture. They seemed to throw their whole body headlong, and stopped only with difficulty. Tests of muscular strength, as for example by the methods of Barré, showed weakness, just as did tests of muscular tonicity. The knee jerks were absent. The folds of the buttocks tended to be shallow.

Mental form. Patients with the mental form, whose gaze was dull and apathetic, were entirely disoriented. They answered questions in monosyllables and only after a certain delay. Weakened to an extreme degree, they collapsed on their straw mattresses. The states of mental confusion and of amnesia were impressive. Even when convalescence was advanced, the slowness of the mental processes was striking. Spasmodic laughing or crying was often observed. In some cases, in the ataxic phase preceding death, bulbar manifestations and symptoms of meningeal irritation were observed.

Lumbar puncture of the comatose patients disclosed nothing pathologic except a slight Claude's hypertension. Lumbar puncture was contraindicated, however, in such of these patients as were already in shock and suffering from circulatory abnormalities.

Conclusion. It is certain that a more protracted study will enable us better to differentiate the various forms we have mentioned and to add others. But these forms were experienced in every camp, with one form or the other predominating according to the geographic location of the camp or to the origin of the internees. The determination of these clinical categories is extremely important for the prognosis and treatment of the patients, as well as for the purpose of scientific research.

Development and Termination

Starvation led naturally to death, unless there was drastic intervention. Cold, hazardous hygienic conditions, restrictions of freedom of movement and lowered morale hastened the fatal outcome.

The meticulous observation of the different modes of death was highly instructive from the pathological point of view. One was impressed by the abrupt transition from an apparently normal state, when the patient attended to his business, to a coma that was followed by death after a more or less short interval. In other cases the patients were attacked more rapidly, in full career, as it were, and collapsed while walking or passed away in their sleep. In some other cases they expired slowly with all the signs of a progressive asthenia.

Death caused by pre-existent or contributory illnesses is not discussed here.

The chief physician of the camp at Vernet could find nothing worthy of note macroscopically in connection with the several autopsies that he had performed, except the existence of cerebral edema in some cases.

It is an interesting fact that the more experience one acquires, the less possible it becomes to predict, through persistent observation of a severe or even a hopeless case, the approximate date of death, or even to be sure of its occurrence.

During January and February, 1942, there were 45 and 49 deaths, respectively, in Camp I (about 400 internees), and 59 and 38 in Camp II (about

2800 internees). With a few exceptions the cause of death was essential malnutrition.

Complications

Tuberculosis. In one camp, well equipped for this purpose, 2000 x-ray examinations of the chest were made. Thirty cases of pulmonary tuberculosis were discovered. The affected persons were not aware of having the disease. Twenty of the cases were of the fibrosclerotic, nonprogressive type, but in 10 cases the lesions were progressive and in 3 of these there was disseminated tuberculosis.

Cardiac disease. Enlargement of the heart was found frequently among people in their fifties—20 per cent of the inhabitants. It was not ascertained whether the apparent enlargement was due to muscular hypertrophy or whether in some cases it was due to the presence of a pericardial exudate. The aorta was ordinarily transparent along its whole course. It is also worth mentioning that the bronchovascular shadow was particularly marked.

Disease of the bones. In general, marked decalcification of the ribs and of the vertebral column was noticeable; sometimes the bony trabeculae were visible. All these symptoms are typical of the state of malnutrition. They are the signs of an abnormally intense degree of general decalcification and demineralization.

Vascular disorders. Angiospasm of the extremities of the fingers and feet was frequently observed. Certain cases were so pronounced that they suggested a diagnosis of Raynaud's disease, but administration of vitamins, especially of pellagra preventive vitamin, brought about improvement. Freezing of the extremities, sometimes severe, occurred in a considerable number of persons in winter. There were many cases of arcus senilis, and precocious senility was frequent.

Endocrine disorders. Clinical and x-ray findings enable us to say a few words about disturbances of endocrine functions. Lack of equipment, however, has restricted investigations in this particular field.

Hyperthyroidism was rare, but there were a few cases. We plan to study this problem later when we can undertake more systematic research. There were many cases of goiter. The great proportion of pendant or pendulous goiters was astonishing. Thyroid disease was sometimes connected with amenorrhea frequently observed—in 30 per cent of the women. Puberty seemed in young girls to be retarded. In one of the large camps there were 171 cases of amenorrhea in women between the ages of fifteen and forty-five, including the following associated conditions: bradycardia, 21 cases (12 per cent); low blood pressure, 22 cases (13 per cent); high blood pressure, 3 cases (2 per cent); and edema, 87 cases, 47 of them slight (51 per cent).

Adrenal insufficiency was not studied, but the existence of hypotension, hypoglycemia and asthenia awakens interest in an investigation dealing with

these characteristic functional disturbances. The existence of spermatogenic troubles, commonly occurring among the debilitated, assumes more than a theoretical importance in the camps. The presence of genital endocrine troubles makes it probable that the hypophysis is also correspondingly affected. On the other hand, it is undeniable that the not uncommon diabetic internees benefit by the starvation diet. No diabetic coma was observed. The same statement applies to various diatheses.

Prognosis

The characteristic curve of an epidemic of communicable disease shows a progressive increase in morbidity in the first stage following the outbreak, and reaches a plateau as the force of the infection begins to exhaust itself or because of effective measures taken to fight the spread of the disease. In the third stage the number of new cases progressively diminishes.

The "disease of starvation," which imitates these characteristics of an epidemic of communicable disease, has not yet reached its peak in the camps. Systematic investigation reveals each week new precachectic cases and persons newly threatened with this condition. The pathogenic factors are far from having exhausted their scope. It is possible, however, to review the elements that make a prognosis possible.

Sex. The records of the women are especially significant. Their attacks came after a delay of about ten months, and the increasing number of women actually affected by the syndrome of malnutrition illustrates eloquently the general aggravation of the situation. The fact that their caloric needs are 20 per cent less than those of men explains in part why women are better protected against starvation than are men. It seems that by now their resistance has been exhausted and that at present the prognosis for women is worse than formerly.

Seasons. There is a better chance to save a patient during the mild seasons of the year than during winter. Cold aggravates the prognosis because of the weakness and the increase in caloric requirements it causes. Edemas were observed to disappear under the sole influence of warm weather. It is certain that the persons who died in the past winter lost their lives as much because of cold as by reason of starvation. This effect of the cold on the undernourished is a frequent observation and causes among other symptoms an abnormally low body temperature. The occurrence of a large number of often severe frosts, even at the end of winter, is connected with the damaging effect of cold on the circulation.

What has been said about the vasolabile type of starvation explains that these persons are also extremely sensitive to the effect of heat in summer, when the danger of dysentery also lies in wait for them. Thus, the two seasons with extremes of weather are full of danger for the undernourished.

Hypotension. Among the factors of prognosis is hypotension, which, once firmly established, is a more serious factor than is bradycardia.

Clinical types. Among the clinical types the neurological and mental types of malnutrition have the most unfavorable prognosis.

Intestinal complications. The prognosis is very bad when diarrhea makes its appearance, because of the dehydration, demineralization and defective assimilation of food and vitamins that follow in its wake. It is noticeable that its frequency varies greatly in the different camps.

Purpura. The appearance of purpura is an aggravating and alarming factor.

Asthenia. The impossibility of keeping a patient in the standing position for a few minutes calls for great caution in the handling of this disease. It is absolutely necessary to impose strict rest on these patients if one would avoid exposing them to the danger of an accidental death, which may occur after an untimely or unsupervised rising, often in response to orders.

Atrophy. Pronounced atrophy and intense emaciation are inseparable companions of cachexia, and they suggest an unfavorable prognosis.

Therapeutic intention. The chances of recovery depend on the age of the patient, on the season of the year, on a certain number of factors enumerated above, on early treatment and above all on the intensity of the chosen treatment. In contrast to the general belief, there is no state, except the final coma, when the disease is irreversible. In spite of striking loss of weight, profound asthenia and a dangerous general condition of health, it was possible to save, through energetic and persistent therapeutical effort, patients who were considered beyond help. This knowledge has a valuable social significance and seriously modifies all our pathological and therapeutic conceptions.

Hypovitaminoses

The exact role of vitamin deprivation in malnutrition cannot be evaluated at present. Although the signs of insufficient caloric intake — loss of weight, emaciation and so forth — are obvious, clinical research is not yet advanced enough to establish with certainty a causal relation between a certain type of malnutrition and a corresponding hypovitaminosis. Moreover, the need for vitamins varies and depends on individual physiologic factors and endogenous influences that regulate the differences in the absorption and utilization of vitamins. At present we must limit ourselves to a review of the different manifestations of the early stage of starvation, without attempting to establish too definite causal connections among the different groups of facts.

Vitamin C. We have already mentioned some patients with a segmental distribution of petechiae on the back of the hands and forearms. Bloody suf-

fusions of the gums and unusually severe hemorrhages were also described by dentists. It was noticed that the vegetables served in the camps were especially poor in vitamins C and D. Therapy with vitamin C gave satisfactory results in these cases. It has not been possible up to the present to determine the elimination of vitamin C in the urine and to proceed to tests of saturation.

Vitamin D. There are many cases of rachitis among the children. The number of severe forms is not alarming, but there are many painful ones. The proportion of scolioses is large. Luckily most of these patients are not beyond recovery. Careful supervision and systematic and early treatment are indispensable. Caries of the teeth is widely prevalent, but the physicians are particularly struck by the cases of gingivitis and periostitis. In a number of cases the loss of fingernails was checked under the influence of a combined antirachitic, calcium and vitamin treatment.

Vitamin A. Recovery by the use of vitamin A was observed in a certain number of persistent eczemas and trophic ulcers occurring among young people. There were 2 cases of xerophthalmia. In certain cases, night blindness was observed. On account of lack of equipment only empirical methods were used; therefore a precise determination of the percentage of the affected cases was not possible. There were several cases of precocious presbyopia. Sometimes there were striking cases of pallor involving the whole pupil, — 10 per cent of the cases, — although the optic nerve was not diseased and there were no errors of refraction. In the opinion of all the physicians who have examined the internees, the lack of vitamin A is particularly noticeable.

Vitamin B. The good therapeutic results observed in the mental and neurologic cases, as well as in cases of neuroanemia after the administration of vitamin B₁ and brewer's yeast, indicate a lack of vitamin B₁ in these cases. The prevalence of meteorism in almost the entire population of internees is equally striking. Lack of vitamin B₁, hindering the assimilation of food, can be suspected of playing a decisive role in producing this symptom.

It would be interesting to know whether the numerous cases of diarrhea were caused partly by deficiency of pellagra-preventive vitamin. This possibility must be especially considered if a severe enteritis is accompanied by glossitis or aphthous stomatitis. These cases were more frequent than is ordinarily supposed. The sudden disappearance of all symptoms after two days' treatment with the amide of nicotinic acid proves that these disorders result from a vitamin deficiency.

STUDY OF THE NUTRITIONAL SITUATION

It is obvious that the state of functional distress found in the internees is brought about by quantitative and qualitative inadequacies in the food supply. Before starting on the study and interpre-

tation of the nutrient value of the food supplies in question, however, it seems advisable to give a review and a summary of the elementary facts regarding the caloric or energy principles of nutrition. It is sufficient to review briefly the indispensable elements of a normal ration and to compare it with the ration served to the internees in the camps.

The standard figures established by the Committee of the Health Section of the League of Nations in 1936 for a normal daily ration state that an adult of medium weight, at absolute rest, requires a daily ration of 2000 calories. The expenditure of energy of the same person leading an ordinary life without manual labor is 2400 calories. The additional expenditure of the muscles in case of light work amounts to 75 calories an hour, or about 600 calories a day, which gives the total of 3000 calories. When the energy value of the ration — that is, the caloric supply it furnishes — is lower than what is spent, the organism has to draw on its resources to make up the deficit by using up its own tissues.

Nutritional deficiency produces a more or less considerable emaciation, in the first place, according to the degree of insufficiency of the food supply. In order to provide for the unavoidable, minimal physiologic expenditure, the organism first uses up the most calorigenic substances, giving the greatest return combined with the least possible spending — that is, fats. This borrowing from the adipose tissue is not deleterious provided that it does not proceed beyond a certain limit and that the balance of the ration is kept above the minimum.

The menace of malnutrition begins when this supply of fat gives out. The proteins provided by the muscular and organic tissues are then called on to furnish the missing balance. From this point on the emaciation is more conspicuous, because the proteins furnish only 4 calories to the gram, — that is, only half the amount provided by 1 gm. of fatty substance. The attack on the protein reserve brings about the most disastrous consequences, because the organism is compelled to draw its supplementary caloric needs from the tissues of superior importance — the muscles and viscera. At this state, catastrophic emaciation is observed.

It is true that as a result of chronic undernourishment a certain state of adaptation is established in which the energy or caloric output is lower than normal. After a certain time undernourishment diminishes the volume of the body until a smaller amount of food becomes sufficient to supply the body, which has become reduced in size, through loss of protein from the organs and of fats from the adipose layers. But if the supply of calories drops even farther, physiologic adaptation becomes impossible.

Rations lower than 1800 calories a day for adults produce considerable emaciation and functional disturbances of various degrees of severity.

Besides containing a certain number of useful calories, different types of food have specific qualities that can in no way be supplied by other nutritive materials. To secure the normal well-being of the organism one must have a balanced ration containing minerals and vitamins as well as the indispensable minimal quantities of carbohydrates, fats and proteins. Nothing can replace these basic and indispensable elements if the living cell is to function properly.

For keeping up the energy balance of the food ration, the following proportions are customary in the countries of western civilization: 50 per cent carbohydrates, 30 per cent lipids and 15 per cent proteins. Sixty per cent of the protein should be of animal origin.

A one-sided diet causes profound physicochemical disturbances of the tissues and organs: the organism becomes incapable of maintaining the calcium of the body and the mineral balance is destroyed. This explains the bone diseases and edemas of starvation that develop with epidemic-like prevalence among those who are suffering from starvation.

Not all the proteins satisfy the needs of the organism with equal efficiency. No matter how large the supply may be, proteins of vegetable origin especially fail in this respect. Some specific needs can be supplied satisfactorily only by animal proteins on account of their higher content of essential amino acids.

Malnutrition is caused by chronic quantitative and qualitative insufficiency of the food supply. It seems necessary

to emphasize this obvious truth because of certain irresponsible opinions on the subject.

Quantitative Value of Food in Camps

The following is an example of the diet per person served to the internees in one of the camps during one month, from October 1 to 30, 1941.

	grams	calories
Bread	7500	17000
Fat	240	2160
Sugar	480	1960
Pumpkin*	30000	6100
Jam	2225	2250
Sardines	1800	1674
Cheese	200	600
Meat	913	911
Tripe	770	465
Carrots†	3750	1406
Cabbage†	3750	1125
		<hr/> 35651

*Served morning and evening for three consecutive weeks.

†Served morning and evening for one week.

This gave an average daily intake of 1188 calories, comprised as follows: protein of animal origin, 15 gm.; protein of vegetable origin, 37 gm.; fat of animal origin, 12 gm.; fat of vegetable origin, 2 gm.; and carbohydrates, 210 gm. When this record of calories was drawn up, the desiccation of the foods, which, according to competent authorities, causes a loss amounting to 15 to 20 per cent in weight, was not taken into consideration, nor was the fact that sardines, for example, contain 30 per cent of their weight as salt, nor was allowance made for the coefficient of resorption. Taking into account all these considerations, the value of the daily rations did not surpass 950 calories per person.

In another camp the quantitative value of the daily ration per person amounted to 1070 calories on February 26 and to 1092 calories on March 4. There was included in the calculation the additional food rationed out for the cachectic patients by the Commissary Department. This means that the caloric value of the actual average camp fare was about 100 calories less than the figure given. In a third camp the mean caloric value of the daily ration per person (determined by weighing) was 958 in June, 1942. In still another camp the accounts of the Commissary Department showed, on paper, daily rations of 1310 caloric value per person. But by weighing the amount of food found in the bowls of the internees, it was found that the figures were much smaller — that is, 1070 to 1109 calories, with an average of 1077 calories daily per person.

These investigations show that the quantitative value expressed in calories never exceeded 1100 calories daily per person and that it ranged between the values of 950 and 1100 calories from October, 1941, through June, 1942.

We have many documents concerning feeding in Germany and the countries invaded between 1914 and 1918. The situation in the urban communities

in those years was considered critical when the daily intake of protein substances dropped to 40 to 50 gm., the daily ration of fats to 20 to 30 gm., and the supply of calories to 1400 to 1800. The average daily ration for an adult was 2232 calories (Loewy's investigation in 1916). German workers received 2200 calories during the first three years of World War I (Lusk and Codville's investigation). The general loss of weight was caused by the reduction in the consumption of fats.

The lowest figures, still well above those observed in the camps, were found in northern France in 1917-1918. They were 1467 calories (Lambling investigation).

Qualitative Value of Food in Camps

In the camps under supervision, the ration of protein substances does not surpass 30 to 50 gm. daily and is almost exclusively of vegetable origin; the actual daily supply of fat is 8 to 10 gm. The nitrogenous and caloric value of the rations distributed in the camps is by no means sufficient to maintain the protein equilibrium of the organism.

Instead of the normal daily ration of 1 gm. of protein per kilogram of body weight, — that is 60 gm. for a person weighing 60 kilograms, — the camp diet contained only 48 gm. of protein of vegetable origin. Furthermore, instead of the daily minimum of 24 gm. of protein of animal origin the maximum was only 15 gm. The result is a continuous deficiency in nitrogen that, even if amounting to only 9 gm. daily, represents a loss of 3300 gm. of protein a year, or a loss of 16.5 kilograms of muscles and visceral tissue for these patients.

The food supply is deficient qualitatively not only from a purely biologic point of view. Other qualitative factors, such as conditions of freshness, conservation and preparation, make the nutritional picture in the camps even worse. Besides, mass feeding does not allow special attention to individual differences or to needs of a particular state of health, and causes inevitable difficulties.

The great monotony of the diet must also be emphasized. It is well known that the ideal condition for the commencement of malnutrition is to stick to the same diet for a long time. The lack of certain vitamins in the diet is sufficient to cause, within a certain time, characteristic hypovitaminoses. This is exactly the case with the internees.

Owing to the purchase of large amounts of a single food product in season, such as cabbages, pumpkins, turnips, Jerusalem artichokes and carrots, the diet remains unchanged for long periods. The same vegetable appears on the table for many consecutive weeks. Improperly preserved, kept in stock for too long, badly prepared and floating in a disproportionate quantity of liquid, this vegetable, poor in vitamins and salts, causes various disabilities associated with hypovitaminosis. Moreover, a con-

siderable number of internees suffered for a long time or are still suffering from acute or subacute intestinal disorders. It is well known that inadequate intestinal absorption can be the cause of hypovitaminosis even if the supply of vitamins is adequate.

Nutritional Situation outside the Camps

We are indebted to the Nutrition Section of the Institute of Hygienic Research of Marseilles (operated under the auspices of the Rockefeller Foundation) for a study of the nutritional condition of the population of Marseilles. The results of the investigation given are those for October–December, 1941, since the figures obtained from more recent investigations are still unavailable. It is for this reason that figures relating to the same period in the camps were given above. Since then the situation in the camps has become aggravated entirely out of proportion to the nutritional restrictions of the people of the country in general.

Quantitative values. The usual average of calories per person daily in the groups studied among the population of Marseilles from February to September, 1941, was 1735 calories for men and women, and 1565 calories for children between the ages of twelve and nineteen. The lowest figures for a few persons with a particularly small ration were 1600 calories for men (in contrast to 2217, the highest figure obtained), 1400 calories for women (in contrast to 1741, the highest figure obtained) and 1400 calories for children between the ages of twelve and nineteen (in contrast to 2097, the highest figure obtained).

For the period October–December, 1941, the figures for all the groups studied are as follows: 1700 calories for men and women, and 1620 calories for children between the ages of twelve and nineteen. The lowest figures found in the case of some persons in particularly bad circumstances are not given, but the figures for the least favored group do not go below 1764 calories for men, 1509 calories for women and 1610 calories for children between the ages of twelve and nineteen. These records give the impression that the nutrition of the people of Marseilles is nearly down to the German nutritional standard of 1917 and in certain respects is even below it.

As regards nutrition in the camps, the rations of the average citizen of Madrid at the end of the siege during the Spanish Civil War (1937–1939) fell to 852 calories from an average of 1514 calories per person at the beginning of the siege (Grande's investigation).

Qualitative values. If the condition of the internees of the camps is compared with that of the population of Marseilles from the qualitative point of view, it is seen that the latter received a daily ration of 65 gm. of protein for the men and 55 gm. for the women. Twenty-eight per cent of this amount was a true protein — that is, 21 gm. of animal protein (October–December, 1941). What is more impor-

tant, this ration succeeded that of February–September, 1941, which without doubt provided for the minimum essential nitrogen. This is not the case with the internees, who have suffered from nitrogen deficiency for the past two years.

Vitamins and Mineral Salts

The daily supply of vitamins and minerals of the internees has not been calculated in detail. Certain considerations, however, permit an evaluation of the situation. The report on the nutritional situation of the population of Marseilles makes it evident

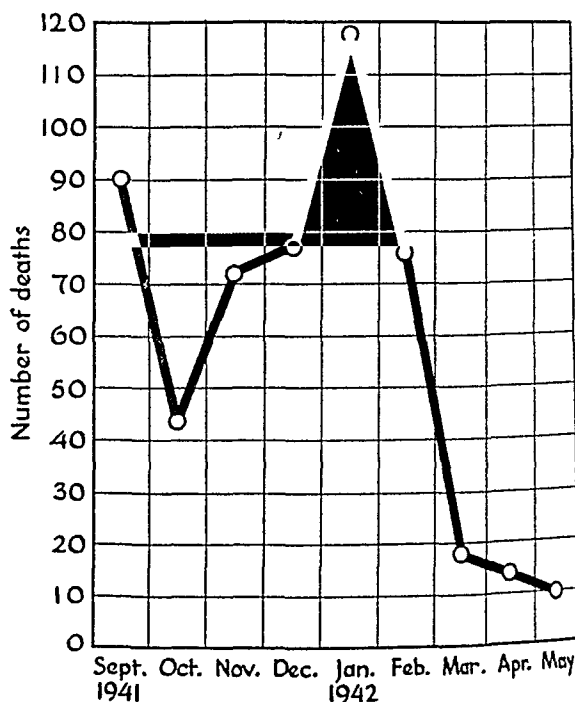


FIGURE 4. Deaths in the Camps during the Last Nine Months.

that there is a lack in the supply of vitamins A, B and C. It is certain, therefore, that the internees in the camps, who receive a diet much poorer in vitamins, suffer an indisputable deficiency in these biocatalysins, a deficiency aggravated by the intestinal disorders prevalent in the camps.

We shall not go into further detail on this question, which has been treated above in the section on hypovitaminosis. Similarly we shall not discuss the starvation that was revealed by the investigation in Marseilles. There was certainly sufficient calcium and phosphorus deficiency in that diet to permit similar conclusions as to the same deficiencies in the camps.

Conclusions

From these comparative studies it may be concluded: that the diet served to the internees in the camps is inferior by 40 to 50 per cent to the diet provided for the civilian population of Marseilles, which, from the point of view of food supplies, is one of the least favored cities in France; that the

prevalence of malnutrition will continue in the camps if the present ration is maintained; and that under the present conditions all effort of the relief agencies to combat malnutrition by an additional food supply and intense treatment with medicines will remain unproductive.

CRITICAL EXAMINATION OF RESULTS

On the whole we may state that the dietary and medical treatment, started in February, 1942, and continued until the present (July, 1942), has en-

through loss of water, and in 8 per cent there was a serious decrease (Fig. 5). Between May 1 and 15, the percentage of the gaining cachectic patients reached 60 per cent and diminished by 17 per cent in the next fortnight. Between June 1 and 15, 51 per cent of the patients gained weight, 19 per cent were stationary, and 30 per cent lost weight, the last being due almost exclusively to the disappearance of edema.

Observations in another camp show the following changes in weight: in March, 27 per cent of the pa-

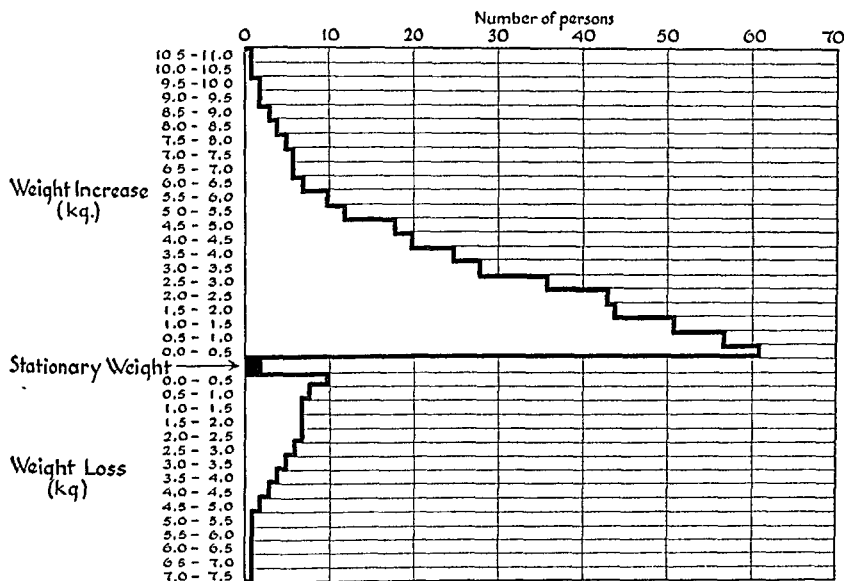


FIGURE 5. *Weight Changes among Cachectic Patients Supplied with Supplementary Nourishment (Camp Rivesaltes: February 27 to May 12, 1942).*

tirely transformed the appearance and state of health of our patients. After three months' treatment one can witness real restorations to health, especially in cases of the neurologic and mental type. The atmosphere of confidence and optimism that at present pervades the barracks of the cachectic patients, formerly desolate, is deeply moving.

Since March, when efficient services and supplies were provided, cases with fatal outcome have practically disappeared from all the camps (Fig. 4). The patients gained in weight; their strength returned.

From April 16 to 30, 1942, of 100 cachectic patients in a certain camp 32 per cent showed increase in weight; in 20 per cent the weight remained stationary; in 40 per cent the patients lost weight

patients showed decreases, 14 per cent were stationary and 60 per cent gained weight; in April, the respective figures were 18, 18 and 64 per cent; and in May, 49, 18 and 33 per cent. The results in May were much less favorable than those in the previous months, because 79 new patients (25 per cent) coming either from prisons or from the camps had to be admitted either to the hospital or to the barracks, and also, because the insufficiency of the food provided by the camp management reached catastrophic proportions during that month; the basic food was reduced to lettuce and turnips, there being no dry vegetables, potatoes, or noodles. In addition, the use of large quantities of salt fish (salted sardines) by the management caused extensive intestinal disorders, from which the patients recovered

with great difficulty. Nevertheless, 37 cachectic patients (5 per cent) were able to leave the hospital after a two-month treatment and are considered to be out of danger for the time being.

This example of the harmful effect of an insufficient and unbalanced diet is not unique. The insufficiency of the usual fare in the camps should make one cautious regarding long-range prognosis. This alarming situation is evident from the progressive increase in the number of cachectic patients and in the decrease of the convalescents. Cachectic and precachectic patients sent back among the other internees relapse into their former condition, because they are exposed to the very factor that caused their disease — insufficient food. The noncachectic persons in their turn swell the number of the cases of malnutrition after exhausting their reserves and becoming more and more sensitive to the same pathogenic factor — starvation. Thus, men wrested with the greatest effort from the effects of starvation have been granted only a postponement of death.

The basic food, the daily ration furnished by the camp, remains the essential element of rescue for patients suffering from starvation, and it is up to the respective authorities to provide it.

* * *

We know that the victims of the "disease of starvation" in the camps number no more than the loss of a few companies in a skirmish, and that thousands of men fall throughout the world — innocent victims of this global war. But we know also that we have not the right to contribute to the depreciation of the value of human life. Our country will never command enough power over the spirit of man to bear the incalculable consequences of useless and unjustifiable deaths. We demand that the relief agencies continue their efforts on behalf of those interned, cost what it may. We appeal to the heartwarming sympathy of the Inspector General of the camps, who has given evidence on numerous occasions of his desire to increase the efforts intended to obtain an effective control of the sources of supply and their regular distribution to the camp subdivisions themselves. The rescue of the interned population is the prize at stake. In their name we express our deep gratitude to all our friends far and near who, by their constant evidences of sympathy, have allowed them to keep inviolate their confidence in human solidarity and their faith in a more just and generous future.

OBSERVATIONS ON THE MASSIVE-DOSE ARSENOTHERAPY OF EARLY SYPHILIS BY THE INTRAVENOUS DRIP METHOD*

IV. Three Years of Trial

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IN March, 1942, Sadusk et al.¹ reported on a series of 33 patients with early syphilis treated at the New Haven Hospital with massive-dose arsenotherapy by the intravenous drip method. It is now possible to give a further follow-up on these patients, as well as toxicologic and therapeutic observations on 40 more.

Since the introduction of massive arsenotherapy for early syphilis by Chargin, Leifer and Hyman² and their associates, numerous modifications of their methods have been tried. They originally demonstrated that the toxicity of a substance such as an arsenical, intravenously administered, is materially lessened if it is introduced by slow, constant drip rather than in a single large injection. Their successful therapeutic results in syphilis have stimulated many others to adopt the administration of massive arsenotherapy. A list of some of these appears in a recent review article by Reynolds, Mohr and Moore.³

Some of these investigators, however, have used drugs that are more toxic than the recommended Mapharsen (meta-amino-para-hydroxy-phenylarsine-oxide hydrochloride), and some have discounted the rationale behind the slow administration of the drug and have administered large doses by the multiple-syringe method. Toxic reactions encountered with the use of neoarsphenamine or the multiple-syringe technic should not reflect on the value of the constant-drip method with Mapharsen.

TECHNIC

Studies of the patients in this series were made to establish a definite diagnosis of early syphilis and to exclude patients with serious complicating disease. The diseases considered contraindications to massive arsenotherapy were liver disease and severe nephritis — the former because arsenicals are taken up and stored mainly in the liver, and the latter because a rare case of renal damage has been reported.⁴ Gonorrhea is not a contraindication, and 1 of our patients had early tuberculosis and another mitral stenosis and an old hemiplegia. Routine studies in-

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Leukopenia was a rare occurrence and was not accompanied by granulocytopenia. A mild secondary anemia was frequently noted during the follow-up period. In most patients no symptoms were referable to the anemia, which subsided without therapy.

Some noted a feeling of tiredness or weakness for two or three weeks.

Electrocardiographic changes⁵ consisted of diminution of the amplitude of the T waves in any or all leads. If the T waves were low at the beginning of therapy, inversion frequently occurred. Such changes disappeared during the first three weeks of the follow-up period, and during the second course of treatment; there was significant depression in only 1 of 3 patients.

During the second or third week after completion of treatment, evidence of peripheral neuritis was noted in nearly half the patients. In most of them it amounted only to numbness and tingling of the toes or rarely of the fingers. This subsided in a few days. A few patients also had definite stocking-type hypesthesia to pinprick. Some, in addition, lost the ankle jerk.

All the above phenomena are considered to be fairly benign accompaniments of treatment. Some are annoying and some cause pain or distress, but none represent cause for alarm.

Of the more serious toxic phenomena, only motor neuritis and jaundice have occurred in this series, and in only 1 case. This patient recovered. Treatment in her case probably represented an error in judgment, since it is likely that she had hepatitis before treatment and was consequently unable to excrete the large doses of Mapharsen. It is for this reason that we hesitate to administer the treatment to any patient with fever unless liver disease can be excluded by appropriate tests.

No patient has had a nitritoid crisis, nephritis, cerebral symptoms, hemorrhagic encephalitis or exfoliative dermatitis, and there have been no fatalities.

THERAPEUTIC EFFECTS

The local primary and secondary lesions became negative on dark-field examination within twenty-four hours from the beginning of treatment. Before the five days were completed there was usually clear evidence of epithelialization and shrinking of the chancre or condyloma. Skin rashes faded more slowly if pigmentation had occurred.

Reversion of the serologic reaction to negative usually occurred during the first six months following therapy, and in most cases between the tenth and twentieth weeks, as shown in Figure 1, which records the rate of reversal in 48 cases in which there has been time for them to become seronegative. In interpreting this figure it should be recalled that in most cases observations were made not oftener than once a month and that, therefore, the elapsed time shown tends to be longer than the actual time of reversal.

In the total series of 72 cases, in which, as stated, 1 patient who was reinfected and treated twice was counted as 2 patients, 36 have been followed for less than six months. (Table 3). Five of these when

treated had primary syphilis with a positive dark-field and a seronegative reaction. These 5 patients, and 12 who were originally seropositive, were seronegative when last seen. Two have had doubtful reaction and 17 are still seropositive, but they must be observed longer before it can be determined whether one course of treatment will cause reversal of the serologic reaction.

There remain 38 patients who have been observed for more than six months (Table 3). Thirty of these became seronegative after one course of

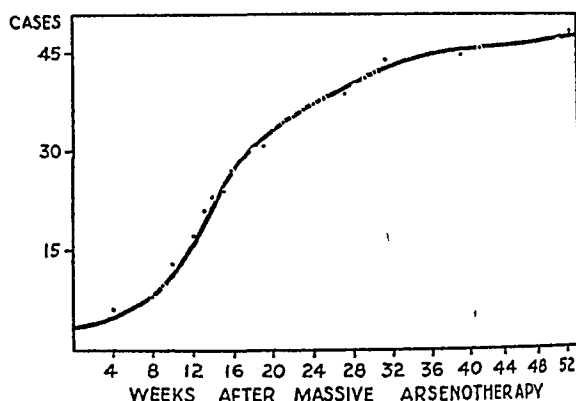


FIGURE 1. *Time of Reversal of the Serologic Reaction.* This chart includes the 48 patients whose serologic reactions became or remained negative after one course of treatment. The curve indicates the cumulative number of seronegative patients at various times during the first year of observation after the administration of massive arsenotherapy.

massive arsenotherapy and have remained so to date. One additional patient became seronegative but relapsed. Seven remained seropositive. The patient who relapsed and 5 of the 7 who remained seropositive, as well as the patient who was reinfected, were given a second course of massive arsenotherapy. The diagnoses at the time of re-treatment are listed in Table 1. Re-treatment is customarily recommended if the serologic tests remain positive after six months of observation or if a relapse or re-infection has occurred.

Following the second course of treatment, both the patient who was reinfected and the one showing a serologic relapse became seronegative. Of the 5 re-treated patients who remained seropositive after the first treatment, 1 has remained seropositive for more than six months after the second treatment and represents an unquestioned serologic failure; 2 are now seronegative, and 2 have not been followed long enough after the second course to determine whether re-treatment will be successful. Two of the 7 patients who remained seropositive after the first treatment have not yet been re-treated. There remain, therefore, 5 of the 38 who have been followed more than six months who are still seropositive, whereas 33 are now seronegative. It should be emphasized, however, that of these 5 patients none show clinical evidence of syphilis and 4 have had

negative spinal-fluid Wassermann reactions. One has had a positive or doubtful spinal-fluid reaction — a twenty-one-year-old seropositive man who had a chancre and a positive dark-field test. Thirty-six weeks after massive arsenotherapy the spinal-fluid Wassermann reaction was negative. Because the patient remained seropositive, however, he received a second course of massive arsenotherapy after fifty-nine weeks. At seventy-one weeks, when he was still seropositive, the spinal fluid gave a positive

limited to the 1 patient with jaundice, severe anemia and motor weakness, who recovered.

This method is not a cure-all for syphilis. We have attempted its use in no patient with latent syphilis unless the secondary eruption was known to have recently been present. Consequently we have no experience in its use in late syphilis. In early syphilis its therapeutic effects as presented above are probably comparable to those obtained with a year and a half's uninterrupted weekly injections by the alter-

TABLE 3. *Therapeutic Results.*

DURATION OF FOLLOW-UP	LATEST SEROLOGIC REACTION			FOLLOW-UP SPINAL-FLUID EXAMINATION			OTHER SIGNS OF SYPHILIS
	NO OF CASES	POSITIVE	NEGATIVE	NO OF CASES	POSITIVE	NEGATIVE	
Less than 6 months*	36	19	17	7	0	7	0
More than 6 months†	38	5	33	31	0	30	0
Treated once	32	2	30	25	0	25	0
Treated twice	6	3	3	6	1	5	0
Totals	74	24	50	38	1	37	0

*Includes 5 seronegative primary cases, 1 of which became temporarily seropositive immediately after treatment.

†Includes 27 cases followed for more than 1 year.

Wassermann reaction in two laboratories and a negative one in a third. The globulin test was negative, the colloidal-gold curve was 0000000000, and the spinal fluid showed 11 lymphocytes per cubic millimeter.

The spinal fluid was examined at the time of treatment in 61 cases, and in 58 of these the Wassermann reaction was negative. In 3 cases it was positive at the beginning of treatment, and in 2 of these it

nating block method. One advantage, of course, lies in the fact that every patient completes a full course of treatment, whereas in patients with early syphilis who enter a course of a year and a half's weekly injections, not more than 16 per cent actually receive an adequate minimal course of therapy as defined by the United States Public Health Service.⁷ A second advantage is that the patient is kept in the hospital while infectious and that when he is

TABLE 4. *Results in Cases of Pregnancy.*

NAME	DATE OF TREATMENT	ADDITIONAL ANTISYPHILITIC TREATMENT	CONDITION OF PLACENTA	CORD BLOOD		VENOUS BLOOD		X-RAY EXAM OF BONES	PHYSICAL EXAMINATION
				Kahn	Wass	Kahn	Wass		
B. B.	7 wk before conception	0	Normal	0	0	0	0	Normal	Normal
I. R.	13 wk before conception	0	Normal	0	0	0	0	Normal	Normal
M. G.	5 wk after conception	0	Normal	0	+	0	0	Normal	Normal
R. S.	6 mo after conception	0	Normal						Baby premature*
I. W.	2 mo after conception	0	Normal	0	0	0	0	Normal	Normal

*Baby weighed 3 pounds, 4 ounces, and died shortly after delivery.

subsequently became negative. The third patient has not had a second lumbar puncture. In 38 cases the spinal fluid was examined during the follow-up period, usually after six months but sometimes earlier. In every case except the one mentioned above, the follow-up spinal-fluid Wassermann reaction was negative (Table 3).

Table 4 shows the results of pregnancy in several cases.⁸

DISCUSSION

It is apparent from the foregoing data that minor discomforts and inconveniences during and immediately after a course of massive arsenotherapy by the continuous-drip method are frequent. Serious toxic phenomena were rare in this small series, being

returned to the community he is, and almost invariably remains, noninfectious.

The cost of massive arsenotherapy by the intravenous drip method varies in different communities. Many of the diagnostic procedures we have done are probably unnecessary except for research purposes. The following steps appear to be essential, and from this list the cost may be calculated: seven to ten days of hospitalization (those who have secondary fever remain a little longer than the others); physician's history, examination and observation; at least two serologic tests; a dark-field examination, a blood-cell count, two urinalyses and, occasionally, a nonprotein nitrogen determination and a bromsulfalein, cephalin-flocculation or other liver-function test; materials for infusion (5 per cent

glucose, Mapharsen and equipment); facilities for obtaining serologic tests, preferably once a month for six months and less often thereafter; and lumbar puncture after six months.

SUMMARY

Massive arsenotherapy for early syphilis has not as yet in our limited experience proved hazardous, and presents no great difficulties in administration. The cardinal points to be observed are as follows: establishment of the diagnosis of early syphilis; exclusion of patients with fever, liver disease or severe nephritis; and periodic follow-up visits with determination of whether re-treatment is necessary on the basis of the serologic reaction six months later, or of relapse at an earlier date.

Its virtue lies in the facts that every patient receives an amount of treatment that has been found sufficient for cure in four fifths of the patients; that completion of a minimum adequate amount of treatment does not depend on the patient's returning; and that when the patient leaves the hospital he is noninfectious and in almost every case remains so. Its disadvantage lies in the danger of an occasional severe toxic reaction that may rarely be fatal.

Using massive arsenotherapy by the five-day continuous intravenous drip method satisfactory

results were obtained in 79 per cent of the cases observed six months or more. By re-treating selected cases, the total of satisfactory results has been raised to 87 per cent. Of the remaining 13 per cent, some patients have not been observed long enough after re-treatment to ascertain the final result. Except for a positive spinal-fluid reaction in 1 case, the only evidence of syphilis in these cases is the positive serologic reaction.

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MEDICAL PROGRESS

PHYSICAL THERAPY IN GENERAL MEDICAL PRACTICE*

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IN PREVIOUS reports on physical therapy there have appeared general reviews and summaries limited to the application of physical measures in the treatment of diseases of the nervous system and conditions commonly encountered in surgical practice.¹⁻⁴ The present addition to the series is restricted to a review of the recent literature relating to the physical-therapy procedures found to be of value in general medical practice.

Neurologists, surgeons and particularly orthopedists have long recognized the value of physical therapy in dealing with conditions affecting locomotion, but the internist has less frequently understood and employed these methods. As explained by Piersol,^{5, 6} this is due to lack of adequate medical education in this field and insufficient training to develop skill in application. The public, however, has remained aware of the benefits of physical

treatment and often seeks it from nonmedical sources when denied it by physicians. Those procedures, therefore, that the general practitioner should find useful will be described in relation to their employment in the treatment of common disorders of the various systems of the body.

CHRONIC ARTHRITIS AND ALLIED DISORDERS

Rheumatoid arthritis is the outstanding example of a medical condition in which the proper use of physical measures is of value. In fact, Short and Bauer⁷ state that physical therapy cannot be dispensed with in the treatment of this disease. They further assert that "general measures — including rest of the whole patient and of the joints, along with an attempt to preserve, so far as possible, the function of the articulations and muscles — form the backbone of the treatment of rheumatoid arthritis." At the Robert Breck Brigham Hospital training in body mechanics has been emphasized as being of prime importance in combating the

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tendency toward joint deformities and in lessening the strain on damaged joints.⁸ Postural exercises are at first taught in the supine position. They include deep breathing, rib stretching, contraction of the abdominal and gluteal muscles or the so-called "pelvic tilt." Later, when more activity is allowed, exercises in sitting and standing positions are performed and the proper mechanics of walking are taught.

In order to improve individual joint function, a combination of physical measures are indicated, including thermotherapy, massage, splintage and exercise. Heat is used to increase local circulation, lessen sensitivity and aid in muscular relaxation before exercise.⁹ Radiant-heat cradles or bakers with four 60-watt or 120-watt bulbs may be used, or for home use a single 250-watt clamp lamp, and 500-watt or 1000-watt units in hospitals.¹⁰ Treatments should last from thirty to forty minutes and be given once or twice daily. Moist heat may be applied in the form of hot fomentations. Melted paraffin wax baths are an especially effective method of applying heat to the extremities.¹¹ These baths consist of a mixture of 7 parts paraffin wax to 1 part paraffin oil, which is kept at the melting point (approximately 125°F.) in a double boiler or an electrically heated unit. The extremity is immersed and quickly removed six to eight times until a coating of wax is formed like a glove, after which it may remain in the bath for twenty to thirty minutes. After the treatment the wax easily peels off and may be used again. Warm whirlpool baths in addition to heating effects also provide mild stimulative massage and an opportunity for underwater exercise. Large Hubbard tubs allowing movement of the shoulders and hips under water are extremely valuable, although of course available only as hospital installations. Therapeutic pools may also be utilized to advantage by arthritic patients, particularly when beginning to walk. In the home a daily hot bath or shower is often of value. A safe bath temperature to begin with is 100°F., which may be increased as tolerated. The length of the bath may be gradually increased up to thirty minutes. In an occasional patient, contrast baths appear to give more relief of pain than does the use of heat alone. In this procedure the temperature of the hot water is 100 to 110°F. and that of the cold 60 to 65°F. Seven alternate immersions are recommended, with five minutes in the hot bath and two in the cool, always starting and finishing in the hot bath.⁹ Diathermy may occasionally be employed, particularly for hospitalized patients, but simpler methods that can be used repeatedly with little expense are usually more suitable. Electric heating pads are used extensively by patients, although they frequently become too hot and may cause burns.

Iontophoresis, using drugs such as Mecholyol or histamine, is often useful in securing a hyperemia that is somewhat more persistent than that following

heat, but this is not recommended as a routine procedure.¹²⁻¹⁴

General ultraviolet irradiation in mild, graduated doses may act as a stimulant to appetite and a sense of well-being, but has no known specific effect on the disease. Controlled heliotherapy may be administered for the same purpose, with avoidance of overexposure.⁷

Fever therapy is often of benefit in selected cases.¹⁵ Krusen⁹ has recommended short sessions of about thirty minutes at 101°F. Fever may be produced by use of a fever cabinet or by a full tub bath at a temperature of 98 to 105°F.

Massage is a useful and often neglected procedure that aims to increase local circulation and improve muscle tone. It may advantageously follow thermal applications and precede therapeutic exercises. As a rule only gentle stroking and kneading motions are to be used and direct movements over the joints are avoided, particularly during the stage of acute inflammation.¹⁶

Therapeutic exercises are the most important single physical measure used to improve joint function, although most effective when combined with heat and massage. The active co-operation of the patient is essential for obtaining satisfactory results in mobilizing joints and maintaining musculature. During the early acute stages of inflammation, static or muscle-setting exercises only are used. Active exercises are then carefully graded in intensity; at first they may consist of active assisted motions, and later of voluntary exercise. Resisted exercises are rarely indicated because of the tendency toward subluxation. Passive stretching or manipulation to increase the range of joint movement is also dangerous. Under careful supervision the patient can usually be taught how to stretch the joints actively in correct positions and how to judge the forcefulness of the efforts according to the degree of subsequent reaction, which when consisting of pain or muscle spasm should not last more than an hour or two. The specific joint exercises are to be repeated by the patient on an average three times each day and must be checked by the technician every day at first, and less often when the routine is well learned.

In many cases of rheumatoid arthritis, deformities of joints are present that require special orthopedic attention for correction. The commonest of these are flexion contractures of the knees and hips and the characteristic combination of flexion, hyperextension and ulnar-deviation deformities of the hands. Traction, specially designed splints or a progressive series of casts have been described for correction and prevention of these deformities.^{17, 18} It is particularly important whenever any immobilizing apparatus is used in these cases that periods of carefully administered physical therapy be provided to prevent ankylosis. The details of the combination of orthopedic and physical therapeutic

measures have been well described by Kuhns¹⁹ in his section of Steinbrocker's textbook on arthritis.

Since rheumatoid arthritis has a well-known tendency to chronicity, physical measures that can be utilized in the home repeatedly each day are to be recommended. Recently Treusch and Krusen²⁰ reported a survey of home physical therapy in 229 cases of arthritis, and found that 93 per cent of the patients followed the instructions for home therapy and 65 per cent continued them for three months or longer. They observed that patients with more than one course of instruction were more likely to carry on. Four fifths of the patients were definitely benefited, and two fifths were enthusiastic over the regime.

In hospitals, occupational therapists may assist in the instruction and supervision of patients in exercises or activities designed to improve joint range and muscular strength. This functional type of occupational therapy may be advantageously co-ordinated with physical-therapy treatments. Such co-ordination is best achieved when the physical and occupational therapy departments are directed by a physician specializing in physical medicine.²¹

Physical therapy is of definite value in the treatment of degenerative joint disease or hypertrophic arthritis (osteoarthritis). Moderate heat applied locally and repeated several times daily is effective in relieving pain.²² The methods previously described are satisfactory. Gentle sedative massage, chiefly stroking and light kneading, assists in reducing muscle spasm and pain. Rest of painful joints during the presence of acute symptoms is usually indicated,²³ but is not so prolonged as in rheumatoid arthritis, for the pathologic changes are in the nature of degeneration or aging processes rather than progressive inflammation.²⁴ It is important to maintain the supporting musculature by means of graded active exercises without weight-bearing or resistance, thus avoiding further traumatic effects on the joints. Teaching the principles of correct body mechanics is of prime importance in order to relieve weight-bearing joints of unnecessary strain. Elderly patients with degenerative disease of the joints are frequently found to have osteoporosis of the spine and disabling pain. Black, Ghormley and Camp²⁵ have reviewed a small series of these cases and discuss the differential diagnosis and possible etiologic factors. They recommend the administration of an adequate diet together with additional calcium and phosphorus and vitamin D. For relief of pain short periods of bed rest and local heat followed by sedative massage were found to be effective.

The role of physical therapy in the treatment of infectious arthritis is secondary to the specific measures available.²⁶ In tuberculous arthritis, healing of the local lesion is generally achieved only by ankylosis, so that heat, massage and exercise are contraindicated. General heliotherapy is, however, of

recognized value in curing the disease process systematically, when used in conjunction with rest and hygienic management, particularly in a sanatorium. Artificial sources of ultraviolet radiation may be used if the climate does not permit direct exposure to the sun. Overdosage must be especially guarded against, and in the presence of active progressive pulmonary lesions all irradiation may have to be omitted.²⁷

Gonorrheal arthritis usually responds well to sulfonamide medication or penicillin. In drug-resistant cases good results from combined drug and fever therapy are reported.^{28, 29} The management of artificial fever requires exact technic and experienced personnel. Hospitalization is essential, and the technics to be used are well established.³⁰ The joints that are acutely inflamed are kept at rest, and no attempts at mobilization are begun until the inflammatory process has subsided. At that time mild heat to improve the circulation and graded active exercise usually suffice to restore full joint function in those cases that are promptly and adequately treated medically. In other types of septic arthritis the end results are dependent on control of the infection by the chemotherapeutic measures available, together with surgical drainage in some cases. Physical therapy aids in overcoming the limitation of motion secondary to immobilization and is begun only after subsidence of the septic process. There may be danger in beginning mobilization too early in these cases because the action of the chemotherapeutic agent may mask the degree of inflammation still present.

Hemophilic arthritis associated with an acute hemarthrosis is often very painful and destructive. These joints should be treated by immobilization, physical therapy being ordered only when the bleeding has stopped and the acute inflammatory reaction has subsided.³⁰ Gentle effleurage and adequate assisted active exercise may then be begun, passive stretching or manipulation being avoided.

Anaphylactic arthritis occurs as a manifestation of serum sickness, and as it is self-limited rarely requires any physical therapy other than heat for relief of pain. Neuritis is a somewhat uncommon complication of serum sickness, but may result in paralysis and atrophy of one or more of the shoulder-girdle muscles, particularly the deltoid, trapezius and serratus magnus.³¹ Although the prognosis for eventual recovery in these cases is good, there is a period of six to twelve months of limited shoulder function and pain during which the patients may be benefited by physical therapy. Mild heat and sedative massage are administered for relief of pain and muscle spasm of the surrounding musculature, which is subjected to unusual strain in moving a partially paralyzed extremity, and the atrophied muscles are benefited by electrical stimulation to lessen the degree of wasting and to hasten functional return after neural regeneration.³²

Another type of cervicobrachial neuritis may result from neurocirculatory compression in patients with a tight or spastic scalenus anticus muscle. According to Spurling and Grantham,³³ about 75 per cent of these patients with painful arms and shoulders improve or become asymptomatic after conservative treatment. Hansson³⁴ is of the same opinion and had described in detail corrective postural exercises for the neck and shoulder-girdle musculature. Local application of heat over the scalenus muscle and sedative massage are also advised.

Radicular type of pain in the same location may be associated with osteoarthritis of the cervical portion of the spinal column.³⁵ According to McFarland and Krusen,³⁶ traction with the Sayre head sling usually gives relief. They advocate radiant heat and massage prior to the traction, which is given in the sitting position with a slowly increasing force up to 70 pounds, as tolerated. The head is then slowly rotated and the traction gradually released. Treatments are repeated twice daily for a week or more.

Myalgia of the cervical muscles is another fairly common condition that responds to treatment by physical agents.³⁷ This is sometimes described as an "indurative" headache or as cervical fibromyositis. Minor epidemics have been reported from England and in the armed forces.³⁸⁻⁴⁰ The etiologic factors are not clear. The predisposing factors include occupational strain or poor posture, resulting in fixation of the head and neck in abnormal alignment, vasomotor imbalance and exposure to cold and drafts. In many cases hypersensitive areas are found in muscles and in palpable thickening or localized areas of muscle spasm.⁴¹ Copeman⁴² in a discussion on the etiology of these so-called "fibrositic nodules" observed, that they may appear in the course of infectious diseases such as influenza and may be reactivated by exposure to cold or by trauma and subsequent sepsis and may form the basis of rheumatic syndromes in later life. Treatment of these patients is often highly dramatic in its results. In some patients with acute stiff neck, complete relief is obtained by fifteen minutes of head traction. Other patients respond as readily to local application of heat with infrared radiation or diathermy, followed by stimulation of the muscles in spasm with a sinusoidal current. For patients with more persistent symptoms, Krusen has described the physical therapeutics of fibrositis.⁴³ Procedures to be used are local heat, special friction massage and stretching exercises. The patients are frequently neglected by physicians unacquainted with the procedures of physical medicine, and they turn to the osteopath or chiropractor for relief that could be obtained by recognized methods of treatment. Manipulation of joints is likewise for the most part neglected by the medical profession, chiefly because of the exaggerated claims made by bone setters and others, based on erroneous diagnosis and unscien-

tific analysis of results. Recently Fredette⁴⁴ has presented the indications and contraindications to manipulation and has described the technic of the maneuvers and the aftercare of patients. Intelligently and skillfully used on properly selected patients, manipulation has a definite role as a procedure in medical therapeutics.

The diagnosis and treatment of patients with complaints of backache and painful feet is a difficult and important subject, particularly in the armed forces and among civilians now leading a more active life than customarily. Orthopedic surgeons are usually called on to care for these patients, and the details of methods used in differential diagnosis and in treatment are beyond the scope of this paper. The internist should, however, be familiar with the management of patients with chronic postural strain, which is the commonest cause of backache.⁴⁵ In these cases physical therapy is of cardinal importance, as has been pointed out by Krusen.⁴⁶ Local application of heat, skillfully administered massage and postural and corrective exercises alleviate symptoms in a large percentage of cases, and Jostes⁴⁷ has shown how manipulation may be of value. Nutt⁴⁸ has written an excellent article on painful feet, outlining for the practicing physician the anatomy of the foot with reference to proper bony and muscular alignment and the prevention and treatment of the common varieties of foot complaints. Other articles dealing more with physical therapy in these conditions have appeared.^{49, 50}

DISEASES OF BLOOD-FORMING ORGANS

Ultraviolet rays are the chief physical agent reported as having a favorable influence on some types of anemia. In secondary anemia this effect is limited, nonspecific and far less efficient than are dietetic and drug treatments.⁵¹ A few cases of thrombocytopenic purpura have been improved by carbon-arc radiation.⁵¹ Apperly⁵² has noted an apparent relation between solar radiation and pernicious anemia, finding that the mortality of this disease is inversely proportional to the effective radiation. Peripheral neuritis⁵³ or combined-system disease as a complication of pernicious anemia often requires prolonged periods of muscle re-education, in addition to adequate replacement therapy during rehabilitation.⁵

The influence of ultraviolet irradiation on resistance to infection is controversial and doubtful. Some beneficial action on wound healing has been shown by exposure to solar radiation, including ultraviolet, visible and infrared wave lengths.⁵⁴

ENDOCRINE AND METABOLIC DISORDERS

In a limited number of cases physical therapy is of value in diseases of the endocrine glands and in disorders of metabolism. Gout because of its interference with joint function is a disease in which some symptomatic relief may be obtained by physi-

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cal means. During the acute attack, rest is essential, and the pain may be diminished by use of hot compresses or in other cases with cold applications.⁵⁵ In the intervals between attacks and during recovery from the acute episodes, mild heat and graduated exercises to maintain and improve musculature are of value. Medicinal therapy is of the greatest importance, and several recent reviews^{55, 56} have adequately discussed it.

Exercise is known to improve the sugar tolerance of diabetic patients when participated in to the proper degree. According to Drury et al.,⁵⁷ experimental studies have shown that heavy exercise reduces the ketosis in guinea pigs and man. The help of a physical therapist, however, is usually not needed in supervising exercise for diabetic patients. Neuritis may be an extremely painful complication of diabetes; these patients are benefited by local hot applications or radiant heat. In the event of pronounced muscular weakness, muscle re-education in the form of specific strengthening exercises may be indicated.³

Obese patients are frequently referred to physical-therapy departments for measures to reduce weight. Passive procedures such as massage or vibration, although popular with the laity, do not remove fat deposits. Dietotherapy is of fundamental importance, but often exercise is prescribed in addition, to increase the caloric requirements of the body at the same time avoiding if possible increase of appetite. Heat treatments, such as cabinet baths or steam baths, temporarily reduce weight through dehydration but are not of permanent value. Cawadias⁵⁸ maintains, however, that obesity is often not controlled by thermodynamic considerations alone, and recommends that the psychologic reactions of the patient be taken into account. He believes that a combination of therapeutic procedures, including so-called "tonic dosage" of ultraviolet rays or hydrotherapy aimed at improving the psychologic balance, is most satisfactory.

Billig⁵⁹ suggests that dysmenorrhea may be secondary to tightness of ligamentous structures concerned with pelvic motion in patients with postural defects. The cyclic nature of the pain is explained by restrictions of the posterior pelvic tilt, dependent on the estrogenic level. He has found that specific stretching exercises are curative in these cases.

Although some experimental studies have indicated that estrus is influenced by artificial illumination in animals,⁶⁰ little is known at present of practical importance concerning physical agents in the treatment of other endocrine disorders.

PULMONARY DISEASE

Short-wave diathermy is used at times as an adjunct in the treatment of acute or chronic bronchitis and in pneumonia, but in view of modern chemotherapy it seems to have a very minor role. Symptomatic relief of pleuritic pain has, however, been

reported.⁶¹ Its possible usefulness in the treatment of atypical or virus pneumonia is worthy of investigation. Special breathing exercises are of value in relieving dyspnea in asthma,⁶² and preliminary reports indicate favorable results with ultraviolet blood irradiation and with artificial-fever therapy.^{63, 64} Reports have been made of successful treatment of pulmonary abscess by short-wave diathermy, but its real worth is doubtful.⁶⁵ Postural exercises are, however, of value in the prevention and treatment of scoliosis secondary to lung abscess, empyema and thoracoplasty.⁶⁶ In uncomplicated pulmonary tuberculosis, heliotherapy is indicated only after prolonged treatment with rest and hygienic and dietetic treatment, and never in the exudative type. Exposure is carefully graded in the early morning and late afternoon.²⁷ Extrapulmonary complications, however, are favorably affected. Graded exercises and occupational therapy have also a definite place in the convalescence of patients with tuberculosis.^{67, 68}

HEART DISEASE

The rehabilitation of many cardiac patients may be facilitated by suitable physical therapy. Parsons Smith⁶⁹ has described the principles involved and methods to be used. He states that the value of exercise in these patients is based on the improvement of myocardial efficiency from increased stroke volume and venous return. The exercise must be suitable, frequently in the form of occupational therapy. Light general massage may precede exercises, which are at first passive and limited to the large joints, with graduation to resistive exercise walking⁷⁰ and games or activities. The general rule are as follows: no extensive, sudden or prolonged exertion of muscle groups should be allowed; undue exposure or athletic tests should be avoided; exercise should be regulated according to the patient's tolerance; and a suitable occupation in view of the cardiac reserve and the patient's natural inclinations should be found.

Disabilities of the shoulder or hand may occur as a complication of coronary occlusion. Askey⁷¹ believes that this is due to a disturbance of the sympathetic nerves from myocardial ischemia together with an underlying latent arthritis. In his experience the condition was self-limited and treatment was of little avail, although massage was sometimes beneficial. Johnson⁷² has reported changes resembling sclerodactylia following myocardial infarction, and Kehl⁷³ noted Dupuytren's contractures as a sequel to disease of the coronary arteries. These authors also think that the etiologic factor is related to irritation of the sympathetic nervous system and noted little benefit from the usual physical-therapy procedures.

Smith and Kountz⁷⁴ observed 15 patients with anginoid pain of a character suggesting heart disease but actually due to deformities of the

thoracic spine. Postural correction by therapeutic exercise was found to lead to improvement or cure of the symptoms.

DISEASES OF EYE, EAR, NOSE AND THROAT

Otolaryngologists frequently recommend the use of physical-therapy procedures in the treatment of infections of the sinuses, ears and upper respiratory passages,⁷⁵ and a textbook has been devoted to this single aspect of therapy.⁷⁶ In uncomplicated acute upper respiratory infections, especially with involvement of the sinuses, applications of heat are at least of symptomatic value. Infrared generators or short-wave diathermy may be used in conjunction with rest, vasoconstrictors and chemotherapy.⁷⁷ It has been pointed out by Brighton, Snow and Friedman,⁷⁸ however, that short-wave therapy should not be considered in any sense a specific curative agent. They found that it was most beneficial in relief of headache in chronic nonpurulent sinusitis. Teed and Kraus⁷⁹ have studied the problem of dosimetry in ultra high-frequency diathermy and have described an instrument that can be used to measure the dosage of energy applied to the sinuses, whereas in the usual application the technician must be guided almost entirely by the subjective response of the patient.

Williams and Elkins⁸⁰ have described a syndrome that they designate as "myalgia of the pharynx." This is characterized by chronic sore throat, pain on swallowing and occasional attacks of hoarseness, without inflammation of the mucous membranes of the upper respiratory tract. The diagnosis is made by finding on palpation points of tenderness localized in the pharyngeal and laryngeal musculature. These writers comment on possible etiologic factors and recommend certain physical-therapy procedures in treatment. These consist in the use of local heat in the form of short infrared irradiation, diathermy and hot fomentations. Massage, however, is the most effective single agent in treatment and is of a heavy-friction type rather than stroking or kneading.

Ultraviolet irradiation is of proved therapeutic value in lupus vulgaris of the ear and nose and in tuberculous infection of the larynx. Galvanism in the form of ion transfer is sometimes used with zinc sulfate in chronic suppurative otitis media and in allergic rhinitis.⁷⁶

Wiener⁸¹ has written on the use of electrotherapy in ophthalmology. Beneficial effects of diathermy on experimental sepsis were noted, and iontophoresis with adrenalin and Mecholyl were reported as of value. Wiener also describes the deleterious effects of ultraviolet irradiation on the cornea, and explains the action of different wave lengths on the cornea, lens and aqueous and vitreous humors in relation to the relative absorption and transmission.

DISEASES OF SKIN

In the treatment of cutaneous disorders ultraviolet irradiation is the most familiar physical-

therapy measure. Although this source of energy has been used empirically for almost every type of skin rash, it has been found to be of value in a limited number of conditions and to be distinctly deleterious in others. Cipollaro⁸² and Beaumont⁸³ have recently summarized the beneficial effects of irradiation in diseases of the skin. An authoritative review of the subject of ultraviolet therapy has been issued by the Council of Physical Therapy of the American Medical Association.²⁷

The consensus is that ultraviolet irradiation is of definite value in the treatment of a number of dermatoses in conjunction with topical application and general measures. Patients with acne vulgaris are benefited by erythema doses of artificial ultraviolet rays once or twice a week. More vigorous treatment may be necessary in chronic deep-seated pustules and cystlike lesions. In these cases irradiation with pressure from an air-cooled or water-cooled lamp may be used. Ultraviolet irradiation is often used for furunculosis or other pyogenic disorders, but there is no conclusive evidence of any great benefit. It has also been found to be of little value in the treatment of fungus infection. In psoriasis, general body irradiation speeds resolution of the lesions. The combination of tar and ultraviolet irradiation, as recommended by Goeckerman,⁸⁴ has given better results than has the use of the latter alone. This consists in applying a 3 per cent crude-coal-tar ointment at night. The next morning the ointment is wiped off. This is followed by irradiation of the whole body, after which a bath may be taken. When possible the treatment is given daily with a graduated dosage.

Lupus vulgaris is definitely benefited by ultraviolet rays. A combination of local and general irradiation yields the best result. The concentrated carbon arc employed by the Finsen method or compression with a cooled arc lamp is satisfactory, for local use and heliotherapy or an air-cooled quartz-mercury arc lamp for general irradiation.

Regarding the undesirable effects of ultraviolet rays, it is to be noted that patients with lupus erythematosus may be photosensitive and that cases have been reported of the precipitation of disseminated lupus erythematosus by ultraviolet irradiation, with alarming results. Many acute and subacute inflammations may also be made more acute or caused to spread by too vigorous ultraviolet treatment. Some patients are light-sensitive and exposure may produce eruptions such as hydroa vacciniforme and urticaria.⁸⁵ The presence of porphyrin, certain dyes and sulfonamides may also cause photosensitivity. The present knowledge of unusual light reactions has been authoritatively presented in a monograph by Blum,⁸⁶ one of the leading investigators in this field.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 30111

PRESENTATION OF CASE

A forty-six-year-old housewife was admitted to the hospital because of abdominal pain.

The history was unsatisfactory because of language difficulty. She was said to have had asthma for years. About twenty months before entry, following her son's enlistment in the Army, she began to "go to pieces" and soon became weak and was forced to go to bed. She was admitted to a community hospital on two occasions within a period of several weeks, because of difficulty in getting her breath, epigastric pain and weakness. She was told that she had heart trouble. She then entered another hospital, where she was treated for "congestive failure, bronchial asthma and chronic bronchitis." She was discharged against advice on the seventh hospital day. She remained at home for three weeks, during which period she was nauseated, vomited a "good bit of her ingested food," had difficulty in getting her breath and was bedridden. The upper abdominal pain continued. She had blood-tinged sputum on several occasions. There was a weight loss of several pounds over a period of months. There was no history of malaria, typhoid fever, dysentery, rheumatic fever, pneumonia, tuberculosis or diabetes.

Physical examination showed a pale woman in moderate distress. The heart was enlarged. The left border of cardiac dullness was 10 cm. to the left of the midline in the fifth space, the right border 2 cm. to the right of the midsternal line. The rate at times was regular, but there were irregularities, which may have been extrasystoles or due to fibrillation. There was a pulse deficit of 12. The pulmonary second sound was greater than the aortic. The lung fields were resonant, with a prolonged expiratory phase and an inspiratory wheeze. The abdomen was protuberant, and there was shifting dullness in both flanks. A tender mass was felt in the right upper quadrant that extended a handbreadth below the costal margin and merged with the liver. A hiatus hernia was noted in the rectus sheath underlying the umbilicus. There was slight pitting edema of the lower legs and sacrum.

*On leave of absence.

The blood pressure was 148 systolic, 100 diastolic. The temperature was 99.6°F., the pulse 120, and the respirations 28.

Examination of the blood showed a red-cell count of 3,650,000, with 10.7 gm. of hemoglobin. The white-cell count was 8700, with 85 per cent neutrophils. A blood Hinton test was negative. The urine was acid, with a specific gravity of 1.018 and a ++ test for albumin. There were 50 white cells per high-power field in the sediment. The blood sugar was 65 mg. per 100 cc., and the nonprotein nitrogen 16 mg. The serum bilirubin was 0.9 mg. per 100 cc. direct, and 2.0 mg. indirect. The stools gave a ++++ guaiac test. One vomitus was guaiac negative.

X-ray films of the chest showed general enlargement of the heart. The vascular markings and hilar shadows were increased in diameter. The diaphragm was normal in position and showed limitation of motion. No definite evidence of fluid was seen. There was thickening of the interlobar septums between the right middle, upper and lower lobes. A plain film of the abdomen showed an area of calcification in the left side of the pelvis, probably a calcified fibroid. There was ascites, and the liver was slightly enlarged. No definite masses were seen. The splenic shadow was not well visualized. A barium enema revealed no evidence of gross obstruction. The examination was unsatisfactory because the colon had not been previously prepared. An electrocardiogram showed occasional ventricular premature beats. The rate was 110. There was slight late inversion of the T wave in Leads 1 and 2, and slight late inversion of the T wave in CF₅. The R wave was small in CF₂ and CF₄. The premature beats in CF₅ varied in direction.

The vomiting and pain continued, and one vomitus was guaiac positive. On the seventh hospital day the temperature rose to 103°F., the pulse to 140, and the respirations to 35. There were bronchial breathing and egophony, with dullness over the right base. The white-cell count was 28,500, with 90 per cent neutrophils. An x-ray film of the chest showed suggestive mottling of the right base. A throat culture gave few beta-hemolytic streptococci. The patient was given 1500 cc. of intravenous fluid almost daily, and 2.5 gm. of sodium sulfadiazine daily for six days. The stools still gave a ++++ guaiac test. An abdominal paracentesis on the eighth day yielded 4500 cc. of murky, red-brown fluid, with a specific gravity of 1.010. The cell count was 8800 red cells and 1200 white cells, 95 per cent of the latter being neutrophils. No tumor cells were seen. The fluid was not cultured. Abdominal examination revealed a tender right-sided mass extending to the right lower quadrant. A sense of resistance was palpated in the left upper quadrant, but there were no masses. A Miller-Abbott tube was passed with some relief.

On the seventh hospital day the temperature fell to normal, the pulse to 110, and the respirations to 30. The Miller-Abbott tube was three fourths of the way down, and although a few coils were seen in the stomach, the tip of the tube was in the small intestine. A few dilated loops of small intestine could be seen by x-ray, some of which appeared to be proximal to the tip of the tube. The patient continued to bring up bile and gastric contents by mouth. She was given 500 cc. of blood. A peritoneoscopy on the twelfth day revealed a mass in the right abdomen that looked like dilated loops of small bowel. These seemed to be adherent to the peritoneum of the abdominal wall. No evidence of carcinoma was seen. The following day there was icterus of the skin and scleras. The urine gave a ++ bile test. The chest was entirely clear both by examination and x-ray. Sulfadiazine was stopped. The distention continued, and the upper abdominal pain persisted. The white-cell count was 25,000. The van den Bergh was 3.3 mg. direct, and 4.1 mg. indirect. X-ray examination on the fifteenth hospital day showed the tip of the Miller-Abbott tube to be in the jejunum. There were several dilated loops of small bowel. A peculiar shadow of increased density was seen along the lateral margin of the right side of the abdomen, apparently between the bowel and the lateral abdominal wall; this suggested the presence of free air within the abdomen. There was evidence of fluid in the peritoneal cavity.

On the sixteenth day an exploratory laparotomy was performed.

DIFFERENTIAL DIAGNOSIS

DR. LELAND S. MCKITTRICK: I wonder if you know how little the statement concerning the electro-

phragm is high on both sides in all the films, even in those taken previously. There was no marked change in the position of the diaphragm over a period of a month; if she was accumulating fluid in the abdomen, however, the diaphragm should have become progressively higher. The heart shadow is horizontal in the chest, because of the high position of the diaphragm, and appears somewhat larger than it actually is. There is no question about the heart's being enlarged. The enlargement is somewhat general but is greatest toward the left in the region of the ventricle. There is no marked dilatation or deformity of the great vessels, and no evidence of calcification. The calcified gland near the hilum probably represents tuberculous infection at some time.

The barium enema is shown here, and to its appearance is normal. There is no evidence of disease in the colon.

In this plain film taken of the abdomen, there are loops that contain air and some of them are small bowel. I think it is fair to say that they are slightly larger than those that we usually see. There is also a general haziness of the whole abdomen, often seen when there is a considerable amount of fluid. The progress of the Miller-Abbott tube was apparent rather slow. That occurs sometimes when the bowel is partially paralyzed. Whether it was due to that or to poor technic, I do not know. The large amount of gas that you see here is probably in the stomach. Again, there are moderately dilated loops of small bowel. It does not seem as if the obstruction in the small bowel as shown in these films is sufficient to have caused the patient's symptoms. It is not very striking evidence at any rate. About the size of the liver — there was, of course, a rather high diaphragm, and the lower edge of the liver is not very

these two things, as well as a positive guaiac test on the stools. I shall dispose of certain things without hesitation.

Any free air in the peritoneal cavity was probably the result of the peritoneoscopy. The patient had a definite increase in indirect bilirubin, and I suspect that this had something to do with the bloody fluid in the peritoneal cavity. I must, then, co-ordinate a positive indirect bilirubin and heart disease of some kind with the mass in the right upper quadrant, the bloody fluid in the peritoneal cavity and the positive guaiac test in the stools, and I am not finding this too easy. If she had not had bloody fluid, I could make a diagnosis that would satisfy me even though it might be wrong. With this combination I can make a diagnosis that is wrong but cannot have the pleasure of making one that completely satisfies me.

The first diagnosis that should be considered is cancer. The patient was forty-six years old and had ascites, bloody fluid in the peritoneal cavity, a mass in the right upper quadrant and a mass in the pelvis. Carcinomatosis is a logical diagnosis and I cannot talk myself out of it except on one basis. Bloody fluid in the peritoneal cavity due to cancer is usually associated with a lot of excrescences and with fairly obvious carcinomatosis as seen either through the peritoneoscope or at exploration. It is my impression that it most commonly comes from ovarian carcinoma and that large tumor masses usually sprout out here and there in the peritoneal cavity. If peritoneoscopy did not reveal any of these things, then I cannot make that diagnosis.

How about carcinoma of the bowel? The positive guaiac test in the stools, the mass in the right upper quadrant, the secondary anemia and the bloody fluid are suggestive. I cannot, however, make a diagnosis of carcinoma of the bowel and be satisfied. I do not recall that I have seen bloody fluid in the peritoneal fluid secondary to intestinal cancer. I am sure one can get it but there again, I have the same problem of the peritoneoscopy, and I have to drop it.

I might make a diagnosis of a gallstone that has eroded through the gall bladder to form an abscess, but I have to drop that diagnosis immediately because of the bloody fluid. That is definitely out so far as logical reasoning or any experience of mine goes.

I might make a diagnosis of acute pancreatitis, which can cause bloody fluid and make a person quite sick, but this story is too chronic. When pancreatitis causes bloody fluid, one has a fairly acute, dramatic process. This woman did not present that picture, so I must drop that diagnosis.

What else causes bloody fluid and a mass? Torsion of an abdominal viscus will do it, as will some interference with blood supply to a segment of bowel, either due to mesenteric emboli or mesenteric thrombosis. Strangulation of the small bowel and

obstruction will give bloody fluid and a mass. Here again, I cannot happily make a diagnosis of strangulated small-bowel obstruction for two reasons: I do not believe she had an obstruction, and obstruction due to strangulation should have a sudden, acute onset. This type of obstruction may go over into a chronic state, with a mass and abscess with dead bowel that is walled off, but it should have a sudden onset. There is no dramatic onset here that I can pick out.

What about mesenteric thrombosis? Recurrent emboli or thrombi ultimately culminating in death of a segment of bowel with localization and walling off of this dead bowel is entirely within the realm of possibility. The presence of heart disease is quite in keeping with this interpretation. This would also give a positive guaiac test in the stools, but is again a farfetched explanation it seems to me; yet I know it occurs. It is so uncommon, however, that it is a difficult diagnosis to make.

I have almost talked myself out of all the things that I can think of, without arriving at a positive conclusion. I think that this woman had a process in the right upper quadrant that involved the bowel, probably the small bowel. I suspect that there was a perforation and localized walling off of that bowel. If I say that and if I believe that that is what she had, then I have to explain it on the basis either of some fairly unusual manifestation of recurrent torsion ultimately ending in strangulation or of many small, minor insults to this woman's vascular tree ultimately ending in one of sufficient magnitude to cause death to at least a small segment of bowel with a resulting localization around it. She may have had general peritonitis, but there is no reason to suppose that she did. She did not at the time of peritoneoscopy. I do not believe that she had mechanical small-bowel obstruction. I cannot do any better than that.

DR. BENJAMIN CASTLEMAN: Dr. Williams, would you like to comment?

DR. CONGER WILLIAMS: I saw this patient when she first came in. She did not speak English, and we could not obtain a history. I thought, as Dr. McKittrick did, that she had some sort of heart disease, but I did not know what. There was definite evidence that she had congestive failure. There was an inconstant gallop rhythm, a very loud pulmonic second sound, pulmonary congestion, dilated neck veins and peripheral edema. I believed that the peripheral edema might have been due in part to a low serum protein, but it turned out later on that the serum protein was not quite low enough to account for the edema and that she did have several other things pointing to heart failure. So far as etiology is concerned, the only thing that seemed reasonable was hypertension, which was moderate — 150 systolic, 100 diastolic — when she came in, with some indication that it might have been higher in the past. We discovered later that

she had had asthma for some time. But I still thought that the diagnosis of chronic cor pulmonale was unlikely. For one thing, the asthma was not severe enough or of long enough duration to produce it. Also the electrocardiographic findings, which are usually important in making that diagnosis, pointed to involvement of the left rather than of the right ventricle.

She responded to diuretic therapy. I did not see her after the first four days.

DR. MCKITTRICK: I feel prouder of my diagnostic acumen as a cardiologist than as a surgeon at this point.

DR. PAUL ZAMECNIK: Retroperitoneal sarcoma can be silent outside the bowel and produce bloody ascites. It is not likely to produce a ++++ guaiac test, however.

DR. MCKITTRICK: Do you think it could produce bloody ascites without involvement of the peritoneum?

DR. ZAMECNIK: It might be difficult to see a retroperitoneal growth by peritoneoscopy, but it could produce ascites.

DR. REED HARWOOD: One gets bloody ascites with thrombosis of the portal vein, probably secondary to liver metastasis.

DR. CASTLEMAN: I shall read part of the operative note:

There was some free fluid in the abdominal cavity, and the small bowel was densely adherent. One loop of small bowel, estimated to be 60 to 75 cm. long, was completely covered with fibrin. There were small abscesses found between the leaves of the mesentery. The biliary tree seemed entirely normal. After the septic area had been opened up, the wound was closed without drainage.

It was impossible to say what was the cause of the sepsis. The right lower quadrant appeared completely free, although the appendix was not visualized. No diagnosis was made. It was thought that mesenteric thrombosis with partial healing could have produced this picture.

Would you like to say anything more at this point, Dr. McKittrick?

DR. MCKITTRICK: The only thing that I can say is that I still do not know what the diagnosis was. But I am sure of one thing, — and Dr. Castleman will bear me out, — multiple small emboli or thrombi in the mesenteric vessels sometimes do not result at once in bowel necrosis; so that the long history does not exclude this diagnosis. I am still intrigued with the bloody fluid. As to what it was, I have no further comment.

CLINICAL DIAGNOSIS

Carcinoma?
Lymphoma?

DR. MCKITTRICK'S DIAGNOSIS

Local gangrene of small bowel with abscess, probably secondary to thrombotic or embolic occlusion of vessels of mesentery.

ANATOMICAL DIAGNOSES

Mesenteric embolism (arterial).
Infarction of small intestine.
Cardiac hypertrophy and dilatation (? hypertensive type or idiopathic congenital).
Mural thrombi: left ventricle.
Thrombosis of mesenteric and portal veins.
Pulmonary infarcts.
Jaundice.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy showed that this mass was gangrenous, matted together, small bowel, which had resulted from mesenteric arterial embolism. There was also venous thrombosis, which was probably secondary to the arterial thrombosis. The source of the emboli was the left ventricular cavity. The heart was moderately enlarged. We could find no evidence of intrinsic heart disease except that there were numerous thrombi attached to the left ventricular wall in among the trabeculae carneae without underlying infarction, an extremely unusual condition. Ordinarily one sees them in the auricles in a patient with heart failure and fibrillation. To find them in the ventricle without myocardial disease is extremely unusual, but they were without question the source of the mesenteric emboli. There was also an extension of the mesenteric venous thrombosis into the portal vein, and many of the radicles of the portal vein throughout the liver contained thrombi. That in itself was not sufficiently extensive to be the cause of the jaundice, but there were numerous infarcts in the lung, and certainly the combination of infarction of the lungs and liver disease was enough to produce jaundice.

I am still intrigued with the type of heart disease. The coronary arteries were perfectly normal. The cardiac enlargement was probably on a hypertensive basis, but I cannot be sure. The left ventricular wall was moderately hypertrophied but the main cause of the enlargement seemed to be dilatation. The right side was not hypertrophied. I do not believe that it was caused by the repeated attacks of asthma.

DR. WILLIAMS: What did the myocardium show?

DR. CASTLEMAN: It was normal. There was no underlying infection or infarction.

The thrombi were not particularly adherent to the wall, and I wonder whether the treatment that she got for the heart failure — the digitalis and quinidine — might have produced mural thrombi. Does that ever occur?

DR. WILLIAMS: It is difficult to say. It has never been reported, to my knowledge. The reason I asked about the microscopic picture is that in Fiedler's (or "isolated") myocarditis¹ such mural thrombi have been reported as a frequent complication.

DR. CASTLEMAN: There was no evidence of myocarditis. The only other possibility is idiopathic

congenital hypertrophy of the heart in adults, such as the cases reported by Levy.² In these cases there are ventricular thrombi, but in his cases and the two that we have had the heart was enlarged to 600 or 700 gm. Here it weighed about 400 gm.

DR. WILLIAMS: Was the ventricular wall thickened?

DR. CASTLEMAN: Slightly.

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- 2 Levy, R L., and Rousselot, L M Cardiac hypertrophy of unknown etiology in young adults *Am Heart J* 9 178-195, 1933

CASE 30112

PRESENTATION OF CASE

First admission. A forty-five-year-old married social worker entered the hospital because of pain in the back.

Six years before entry she had had an attack of vague gastrointestinal symptoms, with epigastric discomfort and gas. Three years later she had had recurrence of the symptoms as well as occasional sour regurgitations and vomiting. She gradually improved and became essentially well until eighteen months before entry, when she developed pain low in the back and felt extremely tired. She lost about 24 pounds in two or three months. Three months before admission she had had a recurrence of the pain in the back and had also developed epigastric pain. She had had the menopause at the age of thirty-eight.

Physical examination showed a well-developed, well-nourished woman. The heart and lungs were normal. There was marked tenderness without spasm or masses in the left upper quadrant. Examination of the spine was negative, as were the pelvic and rectal examinations.

The blood pressure was 110 systolic, 70 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 4,440,000, with 13.6 gm. of hemoglobin. The white-cell count was 9300, with 57 per cent neutrophils. The urine was negative. The stools gave a ++++ guaiac test.

X-ray examination of the lumbar spine and pelvis showed only some new-bone formation about the lateral margins of the right sacroiliac joint. A gastrointestinal series showed, on the lesser curvature just distal to the angle of the stomach, a 2.5-cm. irregular crater with considerable peripheral swelling.

On the thirty-sixth hospital day a subtotal gastrectomy was done. The pathological diagnosis was colloid carcinoma, with metastases to the regional lymph nodes. Postoperatively there was some pain in the abdomen and back, but this disappeared and she was discharged on the fourteenth hospital day.

Second admission (one year later). Following discharge she had had considerable morning nausea and lack of appetite but had carried on until three days before admission, when she developed persistent pain in the left lower quadrant that radiated to the left side of the back. On the day of admission she vomited once. The bowel movements had not been altered.

Physical examination revealed tenderness in the left quadrant. The pelvis showed marked tenderness on motion of the cervix and in the posterior cul-de-sac and a 2-cm. hard tender mass in the right vault. There was considerable vaginal discharge.

The pulse, respirations and temperature were normal.

The white-cell count was 11,100. The urine showed a + test for acetone, a + test for albumin, and the sediment contained occasional red cells and white cells.

X-ray films of the abdomen and chest were negative. No bone metastases could be seen. An intravenous pyelogram was essentially negative. A vaginal smear showed many *Trichomonas vaginalis*.

The patient's condition improved considerably, and she was discharged on the fourth day.

Third admission (twenty-one days later). Following discharge she had continued to vomit three or four times daily. The vomitus consisted of bile-stained fluid without solid material. She had had some diarrhea. Four days before admission she had an episode of vaginal bleeding. She passed several clots for the next three days and then stopped spontaneously. There was no pain or cramps.

Physical examination showed a thin cachectic woman in no distress. There was moderate tenderness to deep palpation in the entire left abdomen. Pelvic examination showed a normal cervix, a very small uterus and a large round, solid, somewhat fixed, but movable mass in the right vault.

The temperature, pulse and respirations were normal. The blood pressure was 122 systolic, 80 diastolic.

The red-cell count was 3,510,000, with 80 per cent hemoglobin. The white-cell count was 8000, with 56 per cent neutrophils. The urine was essentially negative.

A gastrointestinal series, x-ray films of the chest and intravenous pyelograms were negative.

An operation was performed on the sixth day.

DIFFERENTIAL DIAGNOSIS

DR. GORDON A. DONALDSON: Throughout the course of this case history there is one complaint that persisted — pain in the lower part of the back, which continued as such for one and a half years. For the month previous to the final episode it was more marked on the left side and was associated with left lower abdominal pain and tenderness. This latter type of pain suggests disease in the pelvis.

At first, when I read the abstract, the colloid carcinoma of the stomach appeared to be a red her-

ring. She gave a perfectly typical history for carcinoma of the stomach: she had had vague gastrointestinal symptoms and epigastric discomfort for six years; she had gradually developed epigastric pain, regurgitation and vomiting; and she had lost 24 pounds in weight. There was, however, little anemia, indicating that the carcinoma was probably an early one. She did come to operation and had a subtotal gastrectomy with an uneventful convales-

ing she was able to swallow barium for a gastrointestinal series, which showed a normal upper intestinal tract. Moreover, the genitourinary tract was normal by x-ray. So we have a rapidly growing mass in the right pelvis and pain in the left side.

I wonder if we could see the last gastrointestinal series. Does it help?

DR. LAURENCE L. ROBBINS: No; it does not show the mass particularly well, and most of the films

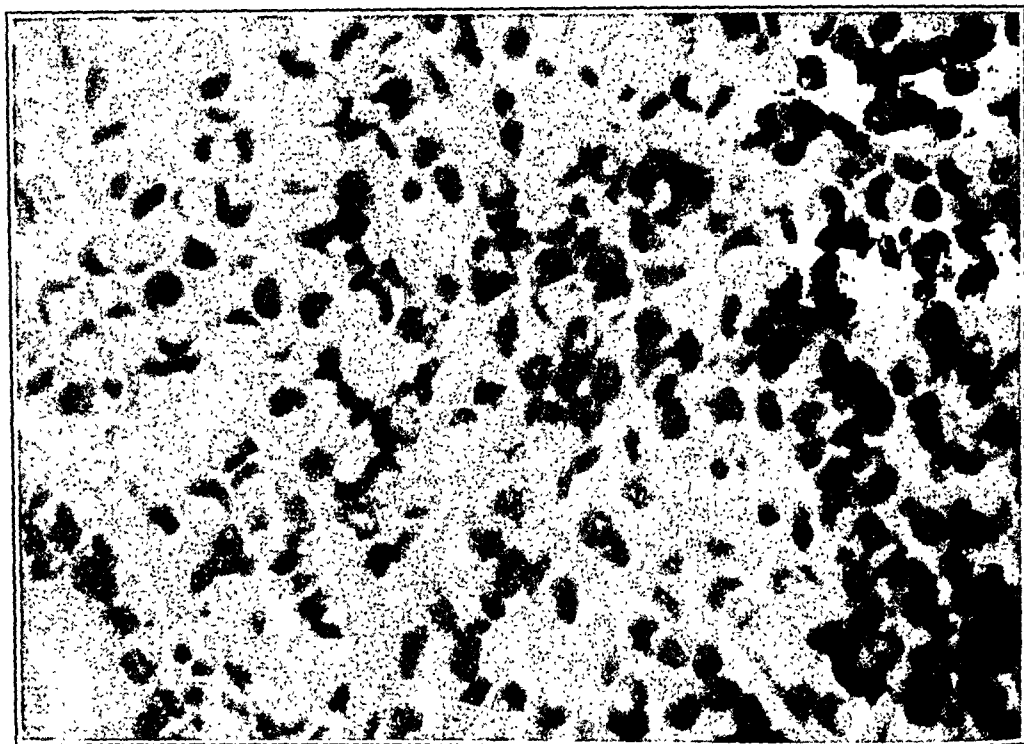


FIGURE 1. *Photomicrograph of the Krukenberg Tumor.*

cence. The regional lymph nodes, surprisingly enough, were found to contain cancer.

Another feature that we note about the first admission is that they were interested in the lumbar spine and pelvis and found that, by x-ray, she did have changes about the sacroiliac joint on the right side. This would help to explain the pain in the back for the previous one and a half years. We must therefore keep in mind the facts that she had a definite pathological diagnosis of colloid carcinoma in the upper abdomen and that she had x-ray changes in the pelvis.

That takes us up to the second and third admissions, at which time attention was directed to the lower abdomen and pelvis. Her pain had changed, being more intense on the left side. She also had a mass on the right side of the pelvis and bleeding. Painless bleeding associated with clots of four days' duration in a woman who is seven years after the menopause is quite significant. I do not believe that the mass was in the gastrointestinal tract, nor do I believe that she had diverticulitis of the sigmoid, since she had no elevation of the white-cell count, temperature or pulse. In spite of the vomit-

ing of the gastric anastomosis and not in the region of the mass.

DR. DONALDSON: I should like to blame all the trouble at the last admission on the mass in the right side of the pelvis. The uterus was described as extremely small—a postmenopausal uterus. So I doubt whether there was anything in the uterus that initiated the bleeding. In addition, the ovaries were normal. This mass could have been the tube, in which case it must have had a tumor. Carcinoma of the tube may cause bleeding, but usually consists of occasional spotting. Such a tumor is rare and is extremely unlikely in this case.

So we come down to the fact that the right ovary was pathologic, and again I do not believe there was any inflammation in the ovary because of the clinical picture. In fact the whole picture fits much better with carcinoma. The patient had anemia and was cachectic. What sort of tumor could this have been? A granulosa-cell tumor could cause her bleeding, but it is usually not massive for four days, and the patient had none of the secondary changes that one generally associates with a granulosa-cell tumor. Also the tumor grew quickly.

rapidly, — a matter of three weeks, — so I rule that out.

Another possibility is a Krukenberg tumor. The patient had a colloid carcinoma of the stomach, the cells of which are histologically similar to those that Krukenberg described, and I think this might well fill the bill. The left-sided pain and fullness in the cul-de-sac could be disease in the other ovary, which was not definitely palpable. Krukenberg tumors are often bilateral. It may not be necessary to say just what sort of tumor this was; but I believe it was a carcinoma of the right ovary, for which operation was undertaken.

DR. JOE V. MEIGS: Our reasoning was similar to that of Dr. Donaldson. When I examined the patient, I was not at all sure that the mass was one-sided. It moved freely with the uterus, and most of us thought that it was connected with the uterus. We had a difficult time explaining why the patient bled. We brought up the possibility of a Krukenberg tumor and advised that she be peritoneoscoped. At peritoneoscopy Dr. Benedict thought that the tumor was a fibroid.

CLINICAL DIAGNOSIS

Fibroid uterus.

DR. DONALDSON'S DIAGNOSIS

Krukenberg tumor of ovary.

ANATOMICAL DIAGNOSIS

Krukenberg tumor of ovaries.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The specimen that we received included a small uterus, almost small enough to be called an infantile uterus, and two large masses, one on the right side, measuring 9 cm.,

and one on the left, measuring 5 cm. The surface of the tumors was smooth and moderately firm. On section the masses showed a firm, smooth, sarcomatous appearance, which is the classic picture of the Krukenberg tumor. In fact when the tumor was first described by Krukenberg* it was thought to be a sarcoma rather than a carcinoma. Microscopic examination showed a signet-ring type of carcinoma (Fig. 1). The uterus had a hyperplastic endometrium, which may have been the cause of the bleeding. We later found out that a vaginal smear showed an estrogen effect, which brought up the possibility, before we knew that there was endometrial hyperplasia, whether such a carcinoma can produce an estrogen effect.

DR. MEIGS: In my investigations of ovarian tumors in women past the menopause I have found that any type of tumor may be accompanied by uterine bleeding. Why, I do not know.

DR. ARTHUR HERTIG: If the stroma of the tumor was involved, it might have produced an estrogen effect. It is a far cry, but it may be analogous to the estrogenic quality of the ovary. I never believed that Krukenberg tumors put out estrogen. Perhaps they do.

DR. MEIGS: I looked carefully and found no evidence of follicle cyst. I have seen Krukenberg tumors that had cysts with perfectly good epithelium, which might secrete estrin.

DR. CASTLEMAN: We did not find any cysts. I do not know why she had endometrial hyperplasia, but that was probably the direct cause of the bleeding.

DR. MAURICE FREMONT-SMITH: The vaginal smear showed *Tr. vaginalis*, which sometimes gives the appearance of an estrogen effect in the vaginal smear.

*Krukenberg, F. Ueber das Fibrosarcoma ovarii mucocellulare (carcinomatodes). *Arch f Gynak* 50:287-321, 1895

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EPIDEMIC STARVATION

THE countries of occupied Europe are faced with potential postwar problems that run the entire gamut of political, economic and social questions of the most vital import. None will be more fundamental or more pressing than those dealing with the nutritional status of liberated populations. In any war, starvation has invariably accompanied prolonged hostilities; conquest and occupation have always caused suffering and want. Mass starvation has rarely, if ever, been distributed so ruthlessly or so systematically to civilian populations as has been the case in occupied Europe in the present struggle. The will to resist has been directly attacked in this total war by all the means possessed

by a force that is purposeful and entirely with conscience. In concentration camps measures have been most systematically carried with results that, for the most part, are still matter of conjecture rather than of carefully documented and exact knowledge. Prolongation of hostilities in Europe through another six to twelve months exaggerate to an unprecedented degree the process of attrition that have been initiated in concentration camps and among civilian population in occupied areas. Reconstruction problems among exhausted survivors will tax to the full the resources of the United Nations if a restoration of health and morale is to be obtained for the victims of tyranny. To what extent mass malnutrition affects postwar thinking on the Continent can hardly be estimated. Since it is certain that chronic nutritional deficiency is not conducive to normal intellectual performance, adequate and carefully planned feeding of European sufferers will be a matter of stern necessity.

The clinical aspects of epidemic starvation are clearly described in the report from southern France published elsewhere in this issue of the *Journal*. The specific manifestations of extreme avitaminosis, protein starvation, lack of hematopoietic factors and insufficient caloric intake, with the modifying effects of intercurrent infection, are graphically presented. Both from the humanitarian and scientific points of view the article is of immediate current interest and should be carefully scrutinized.

RELIGION AND PSYCHIATRY

THE question of the relation, if any, between psychiatry and religion is now and again proposed by someone of speculative mind. The proper approach to such a question might be considered a compliment to the "mental sciences" or it might be looked upon as an attack on the body of knowledge that professes to have insight into the deepest, basic motives of human activity.

Religious belief of some kind or other is as old as human nature and antedates the earliest beginnings of scientific inquiry. Psychiatry is a fairly recent member of the scientific family. Does this

psychiatry, dare or insist on classifying the tendency toward religious belief as founded in phantasy, delusion, wishful thinking? Is religion what Karl Marx called it, "the opium of the people"?

Most psychiatrists are familiar with the criticism that their branch of medicine analyzes its patients' problems, points out weaknesses and frailties and concludes with unhelpful advice comparable to "Now it's up to you." This process supposedly leaves the patient with nothing to stand on or build upon and he must look in other fields if he is to find substantial help in his suffering. It is doubtful that such uninspiring and barren therapy is practiced frequently, and certainly the goal and standards of the best psychotherapy are constructive, not analytic alone. Therapy in psychiatry, as in all of medicine, should include an understanding of the art as well as of the science.

The propounder of the original question may say that this is well enough; perhaps psychotherapy does mean to be constructive, even though he knows of cases in which it was not, but he wants to get down to brass tacks, so to speak, and asks searchingly if psychiatry believes in and accepts the existence of a supreme or supernatural being, God, and in its therapeutic attempts uses this belief or concept in such manner that its patients learn that belief and faith in this existence are essential to their cure.

It may be assumed that they who do have a firm belief in the reality of an infinite being think that such faith is good. They do not berate themselves for having it and they are inclined to think that others would benefit in having the same conviction. They also would say that such trust is not selfish; that, on the contrary, it tends to make them more mindful of others. It is not compatible with religious belief for a person to be thankful that he, anyway, has his salvation whatever happens to the hindmost. The really religious person is concerned about and wants to help others.

Anyone knows, to use that surprisingly inclusive phrase, that being primarily interested in getting the biggest piece of cake for oneself is not good, far-sighted or wise. Psychiatry has found and has taught for years that in so far as the patient's troubles or maladjustments are not due to innate

or organic abnormalities they are dependent on the formative experiences of the early years of life. How a person meets this or that crisis or strain has a direct relation to what he has learned about self-control: to what extent he has gained the perspective which enables him to understand that his egotistic desires and needs may be of minimal importance in a vast universe of time and space.

Psychiatry has always known and taught that having and acting on the knowledge that there is something more important than the self makes for mental health. Geniuses, in varying degrees, may be exceptions, in that their egotistic desires may, in the long run, benefit others enough and more than enough to compensate for the headaches given their immediate associates by their personal idiosyncrasies and selfishnesses.

If good deeds, spontaneously performed, not done because Dale Carnegie says it works, plus a humility that finds others' accomplishments as stimulating, or nearly so, as one's own, plus a perspective out of which comes graceful acceptance of one's own frustrations, plus the conviction that one should do one's job well, whether or not one knows just why — if these sum up to religion, then psychiatry and religion are going in the same direction. If the questioner insists on absolute belief in God as a personality, there may be variance.

There is nothing to indicate that the psychiatrist who does not believe in God does not help his patients. There is nothing to indicate that the psychiatrist who believes in God is a better helper of his patients. Too frequently such a belief is rooted in egotism that cannot face the idea of a universe's going on with one's personal identity gone. It may be remembered, too, that preaching and argument are not always effective. Unostentatious example may carry farther. The old horse-water-drink problem is relevant.

Psychiatry, in therapy, does not want to take away from people their trust in God. It would prefer that they have it or that they achieve it if it can help them. To tell patients, however, that they must have such trust before they can be cured, or to base therapy on such prejudice, even though it might not be expressed in so many words, would be as uncharitable, and often as unprofitable, as

insisting on religious conversion before allowing drink or food to a starving man.

We are at one with God if we are more interested in the welfare of others than we are in personal needs, if the latter are of a kind from which nothing emanates except increased need.

MEDICAL EPONYM

WERNICKE'S DISEASE

The original account of this condition, by Carl W. Wernicke (1848-1905), at that time *Privat-dozent* at the University of Berlin, appears in his *Lehrbuch der Gehirnkrankheiten für Aerzte und Studierende* (Kassel and Berlin, 1881: Vol. II, pages 229 to 242), under the title "Die acute, hämorrhagische Poliencephalitis superior [Acute Hemorrhagic Superior Polioencephalitis]." A portion of the translation follows:

We are here dealing with an independent inflammatory, acute disease of the nuclei of the nerves supplying the eye muscles, which results in death within a period of ten to fourteen days. The localizing symptoms consist in associated ocular muscle palsies, which appear suddenly, progress and lead finally to almost complete paralysis of the eye muscles. Certain muscles, however, such as the sphincter iridis or the levator palpebrarum, are spared. The patients' gait becomes uncertain, showing a combination of stiffness with ataxia, usually suggesting the ataxia of the alcoholic. The general symptoms are striking, and consist in disturbances of consciousness, either somnolence from the outset, or an end stage of somnolence introduced by a more prolonged period of agitation. Further, in all 3 cases there was involvement of the optic nerve, consisting of inflammatory changes in the papilla.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BRADY — William F. Brady, M.D., formerly of Holyoke, died February 28 at his home in St. Petersburg, Florida. He was in his fifty-ninth year.

Dr. Brady received his degree from Tufts College Medical School in 1909. He interned at the Boston City Hospital and at the Providence Hospital, later studying abroad at the University of Vienna. He was elected to the American College of Surgeons in 1937. He was a member of the Massachusetts Medical Society, the American Medical Association and the Holyoke Medical Association.

His widow, his mother and a sister survive.

HOWARD — Margaret E. P. Howard, M.D., of Reading, died March 1. She was in her eighty-fifth year.

Dr. Howard received her degree from the University of Michigan Medical School in 1882. She was a member of the Massachusetts Medical Society and the American Medical Association.

A son and two grandchildren survive.

PALMER — Anna C. Palmer, M.D., of Milton, died February 10. She was in her eighty-seventh year.

Dr. Palmer received her degree from Boston University School of Medicine in 1888. She was president of the Cured Cancer Club and a member of the Massachusetts Medical Society and the American Medical Association.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR FEBRUARY, 1944

RÉSUMÉ

DISEASES	FEBRUARY 1944	FEBRUARY 1943	SEVEN-YEAR MEDIAN
Anterior poliomyelitis	0	0	0
Chancroid	3	*	*
Chicken pox	2754	1279	1438
Diphtheria	26	8	11
Dog bite	592	511	511
Dysentery, bacillary	12	6	6
German measles	188	3491	80
Gonorrhea	390	345	325
Lymphogranuloma venereum	1	*	*
Measles	1875	2661	1896
Meningitis, meningococcal	61	49	8
Meningitis, Pfeiffer-bacillus	2	0	1
Meningitis, pneumococcal	5	3	1
Meningitis, streptococcal	1	0	1
Meningitis, other forms	7	1	1
Meningitis, undetermined	6	4	1
Mumps	1092	1113	777
Pneumonia, lobar	356	323	519
Salmonella infections	1	3	2
Scarlet fever	1777	2080	1002
Syphilis	457	363	374
Tuberculosis, pulmonary	286	165	176
Tuberculosis, other forms	25	14	14
Typhoid fever	1	2	5
Undulant fever	1	1	3
Whooping cough	341	658	779

*Made reportable in December, 1943.

†Pfeiffer-bacillus meningitis only other form reportable previous to 1

COMMENT

Thirteen diseases exceeded the seven-year median du February. Three of these call for special mention: diphtheria meningococcal meningitis and scarlet fever.

Diphtheria has been commented on before. The increase that has been taking place the last few months must be laid, at least in part, at the door of laxness in immunization. Meningococcal meningitis this month reached the point of 61 cases — more than seven times the seven-year median. There was, however, a sizable drop from January's 94 cases. Scarlet fever is following the usual seasonal pattern but at a lower level than that of last year. It is, nevertheless, above the level of the seven-year median.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASE

Actinomycosis was reported from: Fall River, 1; Devens, 1; total, 2.

Anthrax was reported from: Franklin, 1; Peabody, 1; total, 2.

Diphtheria was reported from: Arlington, 1; Boston, 2; Lawrence, 10; Melrose, 3; Somerville, 4; total, 20.

Dysentery, bacillary, was reported from: Beverly, 1; Boston, 2; Worcester, 9; total, 12.

Encephalitis, infectious, was reported from: Holyoke, 1; total, 2.

Hookworm was reported from: Edgartown, 1; total, 1.

Malaria was reported from: Amesbury, 1; Amherst, 1; Boston, 1; Camp Edwards, 3; Cushing General Hospital, 4; Fort Banks, 13; Fort Devens, 25; Gardner, 1; Worcester, 1; total, 50.

Meningitis, meningococcal, was reported from: Barnstable, 2; Boston, 12; Brockton, 1; Cambridge, 1; Camp Edwards, 4; Easton, 1; Everett, 1; Fall River, 1; Fitchburg, 1; Haverhill, 1; Lawrence, 1; Lowell, 5; Lynn, 2; Malden, 1; Middleboro, 3; Montague, 1; Newton, 1; Quincy, 1; Revere, 1; Sharon, 1; Somerville, 2; Southbridge, 1; Springfield, 1; Swampscott, 1; Wakefield, 1; Waltham, 1; Ware, 1; Westfield, 1; Westport, 1; Winchester, 1; Worcester, 1; total, 61.

Meningitis, Pfeiffer-bacillus, was reported from: Boston, 1; Needham, 1; total, 2.

Meningitis, pneumococcal, was reported from: Billerica, 1; Boston, 1; Lawrence, 1; Sutton, 1; Springfield, 1; total, 4.

Meningitis, streptococcal, was reported from: Beverly, 1; total, 1.

Meningitis, other forms, was reported from: Boston, 1; Cambridge, 1; Gloucester, 2; Lynn, 1; total, 7.

Menigitis, undetermined, was reported from Attleboro, 1, Cambridge, 1, Everett, 1, Quincy, 2, Springfield, 1, total, 6
 Salmonella infection was reported from Newton, 1, total, 1
 Septic sore throat was reported from Boston, 10, Camp Edwards, 2, Cushing General Hospital, 1, Lowell, 1, Lynn, 3, Marion, 1, Medford, 1, North Adams, 1, Quincy, 1, Revere, 1, Williamstown, 1, total, 23
 Tetanus was reported from Lawrence, 1, total 1
 Trachoma was reported from Boston, 1, West Newbury, 1, total, 2
 Trichinosis was reported from Boston, 1, Medfield, 1, total, 2
 Typhoid fever was reported from Beverly, 1, West Brookfield, 1, total, 2
 Undulant fever was reported from Oxford, 1, total, 1

WAR ACTIVITIES

PROCUREMENT AND ASSIGNMENT SERVICE

MONEY AID FOR RELOCATIONS

The Washington office of the Procurement and Assignment Service has recently announced that Congress has authorized a fund of \$200,000, to be administered by the United States Public Health Service, for the relocation of physicians and dentists. Payments of \$250 a month for three months as well as the costs of transportation, will be paid to physicians and dentists who desire to relocate, and the officials of the Public Health Service will work in close co operation with state medical and dental chairmen.

MISCELLANY

TUBERCULOSIS AMONG VETERANS

Our national experience with tuberculous veterans of the last war has been unfortunate. Sadder still would be a repetition involving the men and women fighting World War II. The following paper (Dublin, L. J. Function of health officer in control of tuberculosis among veterans. *Am. J. Pub. Health* 33:1425-1429, 1943) addressed originally to health officers, challenges every physician whose practice embraces a tuberculous veteran or the family of one.

During World War I inductions, knowledge and facilities for diagnosis were insufficient to screen out many men suffering from tuberculosis, particularly presymptomatic disease. Thus many active cases entered the Army. Hardships of training and combat produced still more. After the war, care of tuberculous veterans fell to the newly organized Veterans' Bureau. Hospitals and sanatoriums were erected. The service became a major medical activity of the Bureau and of its successor the Veterans' Administration. As early as 1923, a total of 23,653 tuberculous veterans were admitted to treatment in one year. At first, care was limited to tuberculosis connected with military service. Subsequently, cases with disease unrelated to military service became eligible. As a result, tuberculosis admissions have continued numerous. During fiscal 1942, after almost a quarter century, hospital admissions numbered 9658. Over 300,000 such admissions and readmissions have accrued in hospitals of the Veterans' Administration or other government state and civil institutions since the last war.

The government has spared no efforts or funds in erecting and equipping modern hospitals and in providing adequate medical personnel. In March, 1942, there were 217 beds to meet current needs embracing tuberculous veterans of the present war and including tuberculosis beds in veterans' psychiatric hospitals. Besides having all costs of hospitalization and transportation to hospitals paid, tuberculous veterans also receive compensation payments scaled from \$8 to \$100 per month, based on varying grades of dependency, and pay

tempted many to discontinue hospital care and attempt a cure at home. Standards of operation in veterans' hospitals are generous. In 1942, excluding overhead, the per diem cost of operation was \$4.37 per patient and the total direct costs of treatment

approached \$8,000,000. Compensation of World War I veterans with partial or total disability due to tuberculosis, whether or not service connected, amounted to approximately \$40,000,000 during that fiscal year. Such veterans then still numbered 63,000 and exceeded by many times the number accepting hospital care. Disability payments over the last twenty five years aggregate about \$1,000,000,000.

Despite the admirable services available to tuberculous veterans, the experience of their hospitals has been unfavorable. Thus in 1942, of the 9854 cases discharged from these hospitals, only 1.9 per cent were designated "arrested" at discharge with 0.3 per cent "apparently arrested" and 0.8 per cent "quiescent"—a bare total of 3 per cent medically rehabilitated. The remaining discharges included "condition improved" 32.7 per cent, "condition unimproved" 28.9 per cent, "dead" 19.5 per cent, and "condition not stated" 16.0 per cent. The vast majority were obviously not ready for release. So called "improved" cases represent predominantly patients with unstable lesions, a large proportion leaving the hospital without authorization or consent. Thus the Veterans' Administration itself classified the hospitalization of 58 per cent of the cases as "incomplete." These 1942 figures are rather typical, although somewhat worse than those of earlier years.

Exact comparisons among various sanatoriums regarding results of treatment on the basis of such crude figures are impossible particularly now when World War I veterans admitted are older men, usually with chronic disease. Of recent admissions, only 4 per cent were "incipient" cases, 22 per cent "moderately advanced," and 74 per cent "far advanced." Even so, there is a painful contrast between the results with veterans and those achieved in well managed state, municipal and private sanatoriums. In a 1933-1934 survey of tuberculous hospitals and sanatoriums in the United States by the American Medical Association, patients discharged with tuberculosis "arrested," "apparently arrested" or "quiescent" accounted for 29 per cent of all discharged. Among Michigan state sanatoriums from 1930 to 1934 discharges included 61 per cent in these three groups. At Mount McGregor Sanatorium of the Metropolitan Life Insurance Company, of males discharged between 1919 and 1936, and excluding incipient cases, 48 per cent were in comparable categories. Even for cases far advanced on admission, the proportion was 34 per cent.

This deplorable situation among tuberculous veterans has not developed from lack of desire to help the men. Everyone concerned aimed at optimum care. The chief failure was by legislators and others interested in veteran welfare to appreciate fundamental conditions necessary for effective treatment. In part outside pressure was brought to bear to liberalize financial provisions. These measures actually have minimized effective control over the movement of the tuberculous Veterans not subject to ordinary hospital restrictions come and go almost at will regardless of their condition and against medical advice. Patients have been readmitted as many as twenty four different times. Six to eight admissions of the same man are common despite official effort to educate and persuade patients to complete their hospital care and measures to exclude offenders from immediate rehospitalization. Much of the discipline essential to success in treating tuberculosis is lacking. Indeed laws and practices have so evolved that it often financially benefits men to leave the hospital or avoid it altogether. This creates an impossible situation, undermining morale of veterans and professional staff alike.

More serious than mere failure to rehabilitate the patient, discharge before cure exacts its toll on the Nation. It has allowed thousands with communicable tuberculosis to return to civilian communities to live at home or travel about under little or no medical supervision. State and local health officers have assumed little responsibility for men traditionally regarded as wards of the federal government. Few patients have recovered, most have constituted an army of discouraged men spreading tuberculosis in their home communities.

Administration authorities and veterans' leaders are recognizing the need for a remedy, beginning with a drastic change in viewpoint. Specific improvements are being considered and necessary legislative measures will be debated. The American Legion is launching a campaign through its local branches to see that veterans resume and continue hospital treatment until discharged with medical approval.

What is to be done? First, new controls must render liberal benefits medically effective, preventing the drifting of tuberculous veterans until the disease is "arrested" or, at least, not a menace.

Second, the medical profession must co-operate with the Veterans' Administration in the follow-up of tuberculous ex-patients. The Administration has indicated that it will release information to state and local health officers, and routines for getting such reports are imperative. Men still in need of sanatorium care who will not stay in veterans' institutions should be hospitalized in state or local sanatoriums, with legal power invoked where necessary. Each man's circle of contacts should be thoroughly combed for additional cases.

Finally, a genuine effort must be made to protect the large crop of tuberculous veterans inevitable from the present war. It is likely that the Veterans' Administration will function under regulations and procedures governing the care of veterans of World War I. Already, many of the tuberculous veterans of the new war show the same restlessness and abandonment of hospital care that have produced calamitous results among the older men. With new cases already numerous, the stage may be set for another great medical tragedy. Lack of discipline and mistaken generosity may not only take their toll of young men who deserve to get well and resume useful lives, but may seriously delay control of tuberculosis in the general population — unless we act! — Reprinted from *Tuberculosis Abstracts* (March, 1944).

BOOK REVIEWS

Virus Diseases. By members of the Rockefeller Institute for Medical Research. 8°, cloth, 170 pp., with 11 illustrations and 2 plates. Ithaca, New York: Cornell University Press, 1943. \$2.00.

This book consists of six lectures that were delivered by members of the Rockefeller Institute for Medical Research at Cornell University in the spring of 1942. The titles of the lectures were as follows: "Virus Diseases, with Particular Reference to Vaccinia," by Dr. Thomas M. Rivers; "Chemical Structure and the Mutation of Viruses," by Wendell M. Stanley, Ph.D.; "New Hosts as a Key to Progress in Plant Virus Disease Research," by Louis O. Kunkel, Ph.D.; "Swine Influenza," by Dr. Richard E. Shope; "Human Influenza," by Dr. Frank L. Horsfall, Jr.; and "Viruses and Tumors," by Dr. Peyton Rous. Excellent bibliographies are appended to each lecture. An understanding of the contents of this volume is furnished by a quotation from the foreword:

Numerous papers regarding viruses have appeared in scientific journals. Many new virus diseases have been discovered in recent years. Virus workers are not always in agreement and the same virus worker not infrequently changes his notions. Thus, the realm of viruses and virus diseases reminds one of a boom town; nothing is settled. As a result of this confusion, few investigators have had the temerity to write books about viruses. Nevertheless, many facts about these peculiar agents have been established and are sufficiently interesting and important to warrant being brought together under one cover. In this set of Messenger Lectures, six virus workers have attempted to do this for the fields with which they are familiar.

Kaiser Wakes the Doctors. By Paul de Kruif, M.D. 8°, cloth, 158 pp. New York: Harcourt, Brace and Company, 1943. \$2.00.

Paul de Kruif is an enthusiast, and when one reads the writings of such he must be on his guard against being "taken in." There is a seed of truth in most of his writings, but all too often the seed is enlarged into a nonexistent tree.

In reading this book one must admit that the medical care given to the Kaiser employees is excellent. Dr. Garfield and his group have used the best of organized medical facilities to care for the sick and injured among the thousands of employees, the scheme being financed by a prepayment plan in which both employer and employee participate. It differs little from other prepayment plans already in operation, such

as the Endicott-Johnson, the Sante Fe and the Birmingham Coal. The factor of drama that enabled de Kruif to write a book is the sudden growth, which directly paralleled the mushrooming of the Kaiser plant.

This book is not an indictment of existing medical care in the United States. If anything it shows that American medicine under the system of individual initiative can formulate methods for meeting any emergency, and it is doubtful, at least to the reviewer, if any form of bureaucratic medicine could have handled the problem nearly so well as the present competitive system.

Paul de Kruif has read the final report of the Committee on the Costs of Medical Care, in which it is stated that prepayment and group practice are essential. But beyond this, and of greatest importance, is the recognition that the tactics must vary with the needs and facilities of the communities that are to be served. De Kruif has described one method, but in a vast country like the United States no single method will serve. Each small unit must build upon existing facilities to enlarge medical care, and when this is done it may result in a voluntary insurance scheme for covering the costs of medical care, in an industrial prepayment plan or even in direct government subsidy, but not one to the exclusion of all others.

Biochemistry of the Fatty Acids, and their Compounds, the Lipids. By W. R. Bloor. American Chemical Society Monograph Series. 8°, cloth, 387 pp. New York: Reinhold Publishing Corporation, 1943. \$6.00.

The scope of this authoritatively written monograph is best shown by a citation of its chapter titles: "Chemistry," "Digestion and Absorption," "Lipids of the Blood," "Lipids in the Tissue," "Lipid Metabolism" and "Lipids of Secretion and Excretion." The emphasis of the book is on the physiology rather than on the chemistry of the lipids, and it thus makes a valuable guide for those interested in the borderlands of chemical physiology and medicine. The chapter on absorption and the one on blood lipids are especially well conceived and presented.

Oral Diagnosis with Suggestions for Treatment. By Kurt H. Thoma, D.M.D. With contributions by Fred Trevor, D.M.D., Henry Goldman, D.M.D., and David Weisberger, D.M.D. Second edition, revised. 8°, cloth, 495 pp., with 666 illustrations, 63 of them in colors. Philadelphia and London: W. B. Saunders Company, 1943. \$6.75.

The second edition of this book has been revised and renamed, the original edition having been called *Oral Diagnosis and Treatment Planning*.

Additions include a new chapter on wounds and burns, elaboration of the chapter on fractures of the teeth and jaws, and chapters on environmental changes in the teeth and on diseases of partially and completely edentulous mouths, as well as contributions by Drs. Trevor, Goldman and Weisberger on dental caries, periodontal disease and the relation of constitutional disease to oral lesions.

The volume is profusely illustrated, many of the illustrations being unusually clear cut so that even the finer details of the lesions are observable.

The book covers diseases and abnormal conditions of the teeth, jaws and other organs and tissues of the mouth, with suggestions for treatment at the end of each chapter. The arrangement represents a useful and constructive departure from the usual textbook. The therapy both for local lesions and for constitutional and deficiency conditions is brought up to date and given in detail.

The volume is recommended primarily as a textbook for the dental student in the courses covering oral diagnosis or oral medicine, now considered so vital in dental education. As a reference book for the dental practitioner it should stimulate an interest in the relation of oral lesions to disease elsewhere in the body. The physician and medical student could well make use of this book, particularly since oral disease, with its related dental problems, is a neglected field in the medical curriculum.

(Notices on page xi)

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THERAPY WITH FEMALE SEX HORMONES*

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THIS paper is concerned for the most part with functional disorders, since it is almost exclusively in these that hormones are of value. The use of the term "functional" is an admission of ignorance concerning the actual cause and mechanism of a given disability. Irregularities of living — namely, faulty diet, insufficient rest, inadequate healthy activity, changes of environment, strained social relations, absence of healthful routines, shocking episodes, poor emotional adjustment, psychic disturbance, ill-suited occupation, bad habits and so forth — are often obviously, and apparently causally, associated with all sorts of functional disturbances of the various bodily systems for which no organic basis can be ascertained by available methods of study and diagnosis. It is therefore reasonable to assume that these irregularities of living may be more or less involved in the development of gynecologic functional disorders, and indeed careful inquiry often reveals that such is probably the case. Fortunately, many functional upsets are likely to be temporary because they either force the patient to mend her ways spontaneously or to consult some physician who points out her errors of living and the means of correcting them. With exceptions, prescribed and voluntary adjustments of living and constitutional changes over a period of time have more to do with curing patients than has the therapy administered specifically for the complaint. The therapy presumably tides the patient over and sets the stage for cure.

FUNCTIONAL DISORDERS OF MENSTRUATION

Before taking specific steps concerning the patient's presenting complaint, four things should be done. First, well-recognized causes of manifestations similar to those of functional origin must be ruled out. These include amenorrhea due to or associated with congenital anomalies; systemic infections; wasting disease; diabetes; hyperthyroidism;

ovarian, adrenal and pituitary tumors; Cushing's and Fröhlich's syndromes; Simmonds's disease and anorexia nervosa; dysmenorrhea due to pelvic inflammation; endometriosis, adenomyosis and tumors; abnormal genital bleeding due to pathologic pregnancy, cancer, polyps, tumors, inflammations, endometriosis or blood dyscrasias; and sterility due to inflammations, anomalies, endometriosis and tumors; and pathologic entities in the male. Second, the patient should be advised concerning better living habits — those of elimination, rest, activity and occupation — and the adjustment of social problems. Third, the proper medication, such as sedatives, iron and thyroid, should be recommended. Lastly, the elimination of focal infections should be seen to. Prescribing thyroid for patients with the disabilities outlined is more a matter of art than of science. The value of such treatment cannot be measured in terms of the basal metabolic rate and the blood cholesterol alone. Most of those who are studying and treating patients with pelvic symptoms and signs of dysfunction rely on it as a basic part of therapy and are convinced of its value, although it is impossible to explain the mechanism of its effect.

If menstruation does not begin before the age of sixteen, a diagnosis of *primary functional amenorrhea* should be considered, general examination and indicated studies performed, and general treatment begun, as outlined above. If no menstruation occurs by the age of eighteen, this diagnosis is reasonably certain, and efforts at specific treatment may be undertaken. That the amenorrhea is indeed functional can be determined only by demonstrating fundamentally normal genitalia. Without abdominal exploration the diagnosis remains presumptive. Performing an operation simply to prove that the cause is not absent or rudimentary ovaries is hardly warranted. Since there is no tangible benefit to the patient by operation, it seems better to assume that the amenorrhea is functional until the passage of time and the failure of treatment indicate otherwise. Primary and presumably functional amenorrhea is not associated with any other

*Presented at the annual meeting of the New Hampshire Medical Society, Manchester, May 11, 1943.

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unequivocal stigmas of endocrine imbalance. It occurs in normal young women in whom uterine bleeding can be artificially induced.

Secondary or acquired functional amenorrhea, by definition, means that uterine bleeding has previously occurred. That it is not likely to be permanent is attested by the small number of patients seen with this complaint between the ages of thirty and forty. It is unassociated with any other clear stigmas of endocrine imbalance.

An immediate or possible future desire for pregnancy is the main reason for treating patients complaining only of amenorrhea, and in this group may be included those with delayed, skipped and scanty periods. Ovulation is the ultimate aim, although the psychologic value of induced simple bleeding may be great. Unfortunately, ovulation as an immediate result of available therapy cannot yet be promised, but with persistent treatment and the passage of time it may be reasonably expected.

The following treatment is suggested for patients with amenorrhea. Give 1 mg. of diethylstilbestrol orally daily with breakfast for thirty-five days, and 10 mg. of progesterone intramuscularly daily for the following five days. Two to five days after the last injection, a two-day to five-day flow will probably ensue. Counting the beginning of flow as the first day, give 0.5 mg. of diethylstilbestrol daily from the fourth through the twentieth day, and 10 mg. of progesterone intramuscularly daily from the twenty-first through the twenty-fifth day. A period will probably occur around the twenty-eighth day. Repeat the last two steps twice, and then again twice, but reduce the diethylstilbestrol to 0.3 mg. daily. After the next period, give the usual course of diethylstilbestrol daily but omit the progesterone. By that time a spontaneous flow may occur and recur at regular intervals on 0.3 mg. of diethylstilbestrol taken daily, except during flowing. If there is no flow by the thirtieth day, give the progesterone series again.

If after one or more trials with the above schedule of treatment no spontaneity of flow is discernible, it is reasonable to assume that the patient has some basic irremediable defect and that nothing further is to be gained. This therapy is worth trying in patients with Fröhlich's syndrome.

For patients with delayed, skipped or scanty periods, give the treatment described above for the fourth to the twenty-fifth day, and repeat it as seems desirable. So often do these patients have premenstrual distress or tension that this program will be found especially salutary.

Presumably because of variations in intestinal absorption, the orally active anhydro-hydroxyprogesterone cannot be counted on as an effective substitute for injected progesterone. Neither may chorionic, pituitary or pregnant-mare-serum gonadotropins be expected to give predictable results in the above conditions or in the disorders to be dis-

cussed below. Undesirable reactions frequently follow the injection of such preparations. Furthermore, the gonadotropins of animal origin are likely to become ineffective from inducing acquired immunity. The rationale of the above program of treatment is based on the fact that the ovarian steroids have retroactive effects on the anterior hypophysis and that administering them so as to induce cyclic flowing seems to regulate pituitary gonadotropic activity when it is present. It is probable that better regulation would be accomplished if real postovulatory-like menstruation could be produced, but to do this is still impractical owing to the cost of progesterone and the inconvenience of more injections. Recent reports indicate that estrone sulfate (Premarin) may be a more satisfactory oral estrogen than diethylstilbestrol, 2.5 mg. of the former being equivalent to 1 mg. of the latter.

Dysmenorrhea

No clear-cut program for the management of essential, primary or functional dysmenorrhea can be outlined. There are too many variables. Each case presents a different and special problem. Too often have both good and poor results followed exactly similar treatment. If the disability is sufficiently disturbing, a properly executed presacral neurectomy is at present the only means of achieving a cure.

Dysmenorrhea cannot be *cured* by hormones. Temporary relief has been obtained with trials of all the available sex hormones given at various times in the cycle and in various amounts, but the results have been unpredictable and hence not consistently confirmable.

If in the course of managing a case according to one's preference a trial of hormones is elected, predictable although limited benefit may be obtained by the following procedures.

The first of these is to inject 2.5 mg. of estradiol dipropionate intramuscularly on the fifth, eleventh and seventeenth days after the beginning of a period, which prevents the next expected period from occurring. A painful menses usually starts forty-eight to fifty-six days from the onset of the last catamenia. By this technic, half the patient's painful periods can be eliminated.

The second procedure is to give 1.0 mg. of diethylstilbestrol orally daily for twenty doses, beginning twenty-four to seventy-two hours after the onset of menstruation. This is usually followed by a painless flow at approximately the expected interval. Occasionally the expected painless flow fails to appear and in another three or four weeks a painful menses occurs. This treatment, which was worked out by Sturgis,* can be counted on to give complete relief in two out of three cycles. Its main drawback is that not all patients can tolerate the

*Sturgis, S. H. Use of stilbestrol in relief of essential dysmenorrhea. *New Eng. J. Med.* 226:371-376, 1942.

drug, which must be taken as prescribed to produce the desired effect. Diethylstilbestrol also causes vaginal discharge through stimulating the secretion of cervical mucus. It should be employed only as a temporizing measure and not indefinitely.

The third procedure is to administer the male sex hormone, testosterone. This substance is considered by many to be also a female sex hormone. Its place in gynecologic treatment is not yet settled. Some are averse to its employment; others are convinced of its safety and value in the functional disorders of women. My experience with it has been too small to allow an expression of opinion. Relief in about 70 per cent of patients with dysmenorrhea has been reported following various methods of administering testosterone, the simplest being the ingestion of 20 mg. of methyl testosterone daily for fourteen days beginning on the twelfth day of the cycle.

It is evident that alleviation of dysmenorrhea by hormones depends on sufficiently upsetting the patient's own endocrine balance. Hormone therapy, however, does no immediate or permanent harm.

Functional Uterine Bleeding

It is in patients with this disorder in its various manifestations that thyroid is especially beneficial and sometimes apparently curative. Doses approaching tolerance may have to be given.

For those whose catamenias come at approximately twenty-eight-day intervals and are profuse or prolonged or both, 10 mg. of progesterone and 1 mg. of estradiol benzoate (or dipropionate), should be injected simultaneously intramuscularly on the twenty-first day and followed on the twenty-second to the twenty-fifth day by 10 mg. of progesterone intramuscularly. Three cycles of this therapy are usually sufficient.

For the patient whose otherwise fairly normal periods are occurring at too frequent intervals, the previous procedure should be followed, beginning the injections eight days before the anticipated onset of flow and continuing them until the cycle lengthens.

For the patient who is having continuous flowing, 10 mg. of progesterone and 1 mg. of estradiol benzoate should be injected intramuscularly at once and 10 mg. of progesterone daily for the next four days. During this time the bleeding will probably decrease or cease. Two to four days later a fairly normal period will occur. Counting the beginning of this period as the first day, these injections should be repeated beginning on the twenty-first day. Treatment in this manner should be given at least twice, and it may be required again after a lapse. If the patient is bleeding profusely, rapid control is obtained by raising the daily amount of progesterone to 50 mg., reducing the dose as soon as bleeding is less, but in any event continuing injections for five days or even longer until the bleeding stops or

becomes minimal. There will follow the usual hormone-withdrawal flow and then a remission. Cyclic therapy should be continued as described above. At that point the cost of the advocated amounts of progesterone demands consideration. The objection that such therapy is of prohibitive cost may be countered by the fact that progesterone is a true female hormone, effective if given as prescribed, and that its price is being reduced.

For the patient who has a number of days of staining before the catamenia actually begins, the first procedure should be followed if treatment seems desirable.

Marked secondary anemia does occur but is unusual in women with functional flowing. Oftener it intimates the presence of a submucous fibroid, a placental polyp or a subinvolved placental site. Submucous fibroids have occurred so frequently in patients whose anemia seemed out of all proportion to the amount of described and observed flowing as to make one suspect that they may somehow be the cause of the development and absorption of some hemolytic agent. When operation for fibroids with bleeding cannot be immediately undertaken because of undue risk, testosterone propionate in doses up to 75 mg. intramuscularly weekly may be tried, with expectation of some success if a submucous fibroid is not present and of less success if one is present. This hormone is now considered by many to be of value for patients with hypertensive and arteriosclerotic cardiovascular disease. It may come to be a part of the preoperative preparation of such patients when a submucous fibroid necessitates surgery.

The hormonal treatment described is satisfactory for women before they reach their premenopausal years. Examination under anesthesia, diagnostic curettage — followed by careful exploration with a placental forceps, which may catch the polyp missed by the curet — and cervical and endocervical biopsy must, of course, often be performed before the diagnosis of functional flowing becomes clearly acceptable. A burning desire for pregnancy and extreme fear of an induced menopause are the only conceivable reasons for temporizing with the use of hormones in cases of disturbing functional flowing after the age of forty-two. Diagnostic procedures under anesthesia are practically always mandatory, and sterilization by radium at the same time is simple and effective. In fact, the increased safety of major pelvic surgery and the present-day apprehension concerning pelvic cancer, based on the frequent finding of disturbing pathologic changes — anaplasia and areas suggestive of early neoplasia — in the endometriums and cervixes of patients in the fifth decade, and on the insidiousness of adnexal cancer, are at present inducing a preference for hysterectomy and castration to radiation in this age group, especially if there is any other indication for surgery and no forbidding contraindication.

Unfortunately, pelvic cancer has developed often enough at a later date in patients sterilized by radium or x-radiation to demonstrate that this therapy should not be considered prophylactic against cancer.

DISORDERS ASSOCIATED WITH MENSTRUATION

Premenstrual Tension

Premenstrual tension or distress of minor degree is almost universal. Most women are aware of or at least evince by their conduct some of the following troubles to a greater or less degree: premenstrual irritability, apprehension, depression, mental confusion, dizziness, emotional instability, decreased efficiency, easy fatigue, headache, sense of tightness of the head ("head all tied up with iron strings," as one patient recently described it), nasal congestion, sense of abdominal fullness, backache, pelvic discomfort, aching of upper thighs, chilly sensations, swelling and soreness of the breasts, hot flushes and even localized or diffuse edema. When these troubles are disturbing enough, they are considered a clinical entity and given the above appellation.

Since premenstrual tension is more frequent and more severe after the age of thirty-five than before it, the simplest explanation is that it results from the decreased efficiency of aging ovaries in their balanced production of estrogen and progesterone. According to this point of view, it is essentially a part of the climacteric during the premenopausal years, and when it occurs in young women it may be interpreted as a premenstrual imbalance of the ovarian hormones.

The treatment suggested for this condition is to give 0.3 mg. of diethylstilbestrol orally with breakfast daily through the cycle. If relief is adequate, a dose of 0.2 mg. daily may be tried. After three months, treatment may be interrupted temporarily or permanently. No endocrine therapy has yet been worked out for those rare cases of clinically apparent premenstrual and menstrual edema.

Headache

Headache associated with menstruation is often a complaint of patients who are sooner or later found to have endometriosis. In the absence of confirmatory symptoms, signs and findings of this disease, nonincapacitating headaches may be considered and treated as part of the premenstrual tension syndrome. When, however, headaches associated with menstruation are incapacitating, resemble migraine, and yet are not controlled by ergotamine tartrate, the best treatment at present is the intramuscular injection of 1 mg. of estradiol dipropionate seven days before the expected onset of the catamenia.

Mammary Pain and Secretion

Any hormone treatment for breast complaints is emphatically to be restricted to those whose breasts

are engorged, thickened or diffusely nodular. All thought of endocrine therapy must be dispelled when a discrete mass, cystic disease or bloody secretion is encountered. These are surgical problems, with the exception of some cases of cystic change in the breasts of young women. (I recently cared for a patient with a painful cancer of the breast and axillary metastases who had been treated for three months by hormone injections and "ovary tablets.")

The simplest remedy for premenstrual soreness and swelling of the breasts is diethylstilbestrol, 0.3 mg. daily, reduced to 0.2 mg. daily as soon as relief is experienced. Some patients have chronic intermittent bilateral breast pain with premenstrual exacerbation. They are likely to be disturbed mentally, with a "breast fixation." These cases are rare. Testosterone propionate is reported to be effective, and 30 to 50 mg. is given intramuscularly weekly, beginning twelve to fourteen days before the expected period, or even through the month except during flow, for two or three cycles. Re-treatment is usually necessary after one or more months' rest from injections. Delayed periods may occur when male hormones are given during the first sixteen days of the cycle.

The management of patients with nonbloody mammary secretion is still unsettled. Secretion indicates cystic change. When to operate and how much tissue to remove are the problem. In older women simple mastectomy is the easiest solution. Unless all breast tissue is removed, periodic examination for an indefinite length of time is mandatory. In young women the secretion may be temporary, as may the cyst if it is palpable. Mammary secretion, with or without pain, in those for whom surgery does not seem necessary is said to be controlled by testosterone propionate, given as for those with painful breasts.

Midmonth Pain or Bleeding

Functional midmonth pain or bleeding is not a frequent or persistent disturbance. Thyroid is the simplest medication. Methyl testosterone, 5 to 10 mg. being given orally daily, except during menstruation, for three to five months, is said to hasten the disappearance of this ovulation syndrome.

THE MENOPAUSE

Diagnostic pelvic investigation under anesthesia for postmenopausal uterine bleeding has been more frequently required since diethylstilbestrol became the generally preferred estrogen for the treatment of the climacteric. In addition to the trouble and expense entailed by this development, these patients must be followed with special care to be sure that the flowing did indeed result from the medication, for even after careful examination under anesthesia and findings consistent with hormonal bleeding, one cannot avoid a feeling of uncertainty regarding the possibility of adnexal or intramural

neoplasm. Keeping the daily amount of diethylstilbestrol below 0.5 mg. avoids induced endometrial bleeding and practically always suffices for the control of menopausal symptoms. It is worth while remembering that painful joints are frequently a menopausal symptom that responds rapidly to small amounts of estrogenic substance.

FUNCTIONAL STERILITY

Once the husband has been shown to produce a healthy semen and the wife to have a healthy vagina and cervix, palpably normal internal genitalia, patent tubes, regular menstruation from a secretory endometrium and endocervical mucus containing a fair number of active spermatozoa three to six hours after intercourse, failure to conceive may be considered functional. In these situations, general health measures, as outlined earlier, small doses of thyroid and mild intrauterine trauma or tubal insufflation within a few hours after intercourse at about midcycle every two to three months are likely to be effective without the use of sex hormones. During the last year 3 women with functional sterility became pregnant one to six months after I had temporarily given up hope of success, having for the previous twenty-four to thirty months followed the above recommendations and in addition having employed various hormones in carefully planned trials. This sort of experience makes me diffident about offering advice, and philosophic in my attitude toward the treatment of functional sterility. At the Free Hospital for Women it has been believed for some years that the daily ingestion of moderate doses of an estrogen enhances the wife's chances of pregnancy, and 0.1 to 0.2 mg. of diethylstilbestrol is now commonly prescribed. A study of the literature indicates that there is as yet no specific hormonal means of increasing fertility in the husband. For him the best treatment appears to be an active out-of-door vacation, in addition to general health measures and the giving of thyroid.

Functional sterility sometimes exists because the wife is having anovulatory cycles, as indicated by failure to find secretory endometrium on biopsy at the beginning of flow, in which case injections as described above in the first procedure under "Functional Uterine Bleeding," should be given until a secretory endometrium is found.

MISCELLANEOUS CONDITIONS

Frigidity

Methyl testosterone, 10 to 20 mg. orally daily, has been reported as effective in those women whose

desire for and satisfaction from intercourse have waned. This medication is also stated to render them more stable emotionally and to make them feel more energetic.

Vaginitis and Pruritus, Kraurosis and Leukoplakia of Vulva

It is customary in reviews like this to describe the use of hormones in these conditions, but there appears to be no routine need for them. Vaginitis usually responds to mechanical cleansing and simple antibacterial and antiprotozoal remedies. Rarely it is necessary to resort to the daily vaginal insertion of 0.5 mg. of diethylstilbestrol for a persistent senile vaginitis.

Pruritus responds to dermatologic treatment if it is due to bacterial and fungus involvement and if the process is superficial. If the process involves the deeper layers of the vulva, and especially if it is localized in the vulval tissues, complete superficial vulvectomy is usually sooner or later necessary. Kraurosis and leukoplakia are likely to require surgery. The histologic changes of lichen planus of the vulva are similar to those of kraurosis and leukoplakia. If lichen planus is sufficiently localized and the irritation from it is not relieved by conservative means, surgery is justifiable.

* * *

For years, of course, the treatment of functional gynecologic disorders has consisted of general health measures, the giving of thyroid and of ovarian extracts and the care of associated conditions, such as anemia and infectious foci. Progress has come from the development of effective preparations of the steroid hormones and diethylstilbestrol, and from the working out of the details of their application.

8 Cumberland Avenue

DISCUSSION

DR. MARION W. WESTERMAYER, Fairlee, Vermont: Is 1 international unit of progestin equivalent in effectiveness to 1 mg. of progesterone?

A MEMBER: Would you give thyroid routinely in all cases of functional disorders, and how much do you use?

DR. W. J. P. DYE, Wolfeboro: A great many women whom I have seen are unable to take stilbestrol by mouth because of gastrointestinal symptoms and even nausea and vomiting. What do you do in this type of case, and do you have the same difficulty?

DR. SMITH (closing): One international unit of progestin is equivalent to 1 mg. of progesterone. Progestin is effective, but the synthetic hormone is cheaper and more easily available.

In regard to thyroid extract, I give it almost routinely to patients with functional disorders, usually in doses of 1 gr. or less daily.

For those patients who suffer gastrointestinal disturbance from stilbestrol, I am now changing to estrone sulfate. It costs a good deal more, but so far I have found it worth while.

METHODS OF DIAGNOSIS OF JAUNDICE*

FRANKLIN W. WHITE, M.D.†

BOSTON

A STUDY of the errors in diagnosis has already been reported¹ in 500 cases of jaundice that came under our observation on the Second and Fourth Medical Services at the Boston City Hospital during the last six years. In the present paper the clinical and laboratory methods that proved most useful in the diagnosis of these cases are reviewed. This series included most types of jaundice, such as complete and partial biliary obstruction, acute and subacute infectious and toxic hepatitis, the cirrhososes, — portal, biliary, pigmentary, toxic and cardiac, — fatty liver, tumors and syphilis of the liver, and hemolytic anemia.

On account of variation of symptoms, latent or exceptional cases, multiple diseases in a single patient and the large number of factors that go to make up the clinical picture, the number of possible combinations of symptoms and signs in any given disease causing jaundice is large, and 100 per cent accuracy of diagnosis can never be attained. The diagnosis may be laboriously built up from a collection of clues or may be obvious at once, as in arsphenamine hepatitis, prolonged painless complete obstruction and chronic low-grade familial hemolytic anemia.

HISTORY

The age incidence in four important groups is given in Table 1. In patients under thirty the cases of infectious hepatitis comprised 40 per cent, those of cholecystitis 15 per cent, and those of cirrhosis 9 per cent; there were no tumors. Infectious hepatitis may, however, occur at any age; 12 per cent of the cases occurred in patients over sixty, and the oldest of these, on whom an autopsy was performed, was eighty-seven. The large majority of cases of

TABLE 1. Age Incidence.

DIAGNOSIS	NO. OF CASES	PERCENTAGES		
		UNDER 30	30-50	OVER 50
Acute infectious hepatitis	101	40	32	27
Cholecystitis	71	15	31	53
Cirrhososes	161	9	40	51
Tumors of liver and bile passages ..	83	0	19	81

cirrrosis and cholecystitis occurred in middle life, and 80 per cent of the tumors were in patients over fifty. Painless jaundice in youth first suggests infectious hepatitis, and in patients over fifty cholecystitis, cirrhosis or tumor.

The family history sometimes strongly suggested hemolytic anemia, and sometimes gall-bladder disease or cancer.

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The jaundice in the familial hemolytic cases was often slight and chronic — having been present for years. With incomplete obstruction by gallstones it was variable in duration and in degree, owing in part to the ball-valve action of stones in the common duct. In complete obstruction, which was due almost entirely to tumors, it was continuous and progressive over weeks or months until relieved by operation. In acute and chronic hepatitis the jaundice lasted for days, weeks or even months, depending on the degree of liver damage. Rarely a patient with hepatic cirrhosis remained continuously jaundiced for many months. Many patients were poor observers of the onset and variation of jaundice. (See also the paragraph on the depth of jaundice under "Laboratory Tests," below.)

Pain was important in its position, radiation, recurrence, character and relation to the onset of the jaundice. Acute and chronic hepatitis, stricture, hemolytic anemias and tumors are often described as causing so-called "painless jaundice." This is not strictly true. Pain occasionally occurred in acute and chronic hepatitis, and in rare cases was intense, with an extremely tender liver. Tumors often caused some pain, which was especially severe in the pancreas, but brief, sharp attacks of colic requiring morphine and recurring at intervals over weeks or months were much more frequent in cholecystitis and gallstones.

A history of exposure to liver poisons, such as arsenic, cinchophen, chloroform, carbon tetrachloride, gold thiosulfate and so forth, or to an infection at the onset of jaundice, was important.

Fever occurred in infection of the gall bladder, bile passages, liver or portal vein and in late cancer, and also in severe, acute hepatitis. If high and continued it was an extremely serious sign.

The distinction between acute liver disease and acute necrosis in chronic liver disease was sometimes difficult. A chronic portal or toxic cirrhosis may remain latent for so many months or years that the absence of previous symptoms cannot be relied on. Chronic disease was suggested if at the onset gross changes were found in the size, surface or density of the liver, all of which were out of proportion to the mild or moderate acute attack, or if such changes persisted long after the simple attack was over.

The course often aided diagnosis. A short course of moderate to severe jaundice (icteric index, 50 to 200) with marked loss of liver function was more frequently due to hepatocellular damage than to obstruction. The course may also be helpful in differentiating cancer from cirrhosis. If the disease is terminal, death naturally results in either disease;

if it is not terminal, cirrhosis may improve and as a result cancer can be ruled out. Complete obstruction due to cancer almost never improves, but in one exceptional case with an enlarged, hard, irregular-shaped liver the jaundice improved greatly and the gray stools became brown; a cancer of the gall bladder had ulcerated into the colon and had thus relieved the obstruction of the common duct.

Gall-bladder disease proved to be probable in patients in middle life in whom an earlier diagnosis of acute hepatitis or incipient cirrhosis had been made. The Graham test was highly useful after the jaundice had disappeared and the liver function was normal or much improved.

PHYSICAL EXAMINATION

An enlarged liver was a valuable sign of hepatic disease but gave little help in deciding on its type. The liver was usually enlarged in hemolytic anemia, passive congestion, infectious or toxic hepatitis, cirrhosis, tumor, biliary obstruction, abscess, cholangitis, fatty liver and general infections. A distinctly small liver was found in only a few cases of acute necrosis — acute yellow atrophy — or atrophic portal cirrhosis. The density and irregularity of surface was of greater diagnostic value, but opinions were sometimes conflicting owing to the difficulty of feeling the liver through an abdominal wall that was thick, rigid or distended or contained irregularly formed deposits of fat. A granular, dense liver may be described as nodular, but in this series the term was reserved for livers with nodules or irregular-shaped deposits over 1 to 2 cm. in diameter, which were found only in tumors, the nodular hyperplasia of toxic cirrhosis and hepar lobatum. There was no case of tuberculosis of the liver.

Most of the firm livers resulted in a diagnosis of cirrhosis and all the stony-hard ones in a diagnosis of cancer. In passive congestion or fatty liver, a large, smooth organ of normal consistence presented no difficulties in diagnosis.

The smooth outline of an enlarged gall bladder was occasionally lost as a result of adhesions to the bowel, omentum, enlarged lymph nodes and so forth, and the organ resembled an enlarged liver. Tumors of the right upper quadrant of the kidney, adrenal glands, colon and so forth are rarely associated with jaundice.

A dilated gall bladder is said to be found in about half the cases of tumor involving the common duct (Courvoisier's law). In 33 cases of complete obstruction, after ruling out 1 case of cholecystitis, 2 with previous cholecystectomies and 1 in which the obstruction was above the cystic duct, there remained 29 cases of malignant obstruction of the common duct. The gall bladder was palpable on repeated examinations before operation in only 9 of these. A dilated gall bladder is important in diagnosis only if it is felt, and palpation may be difficult on account of ascites or distention. Complete ab-

sence of bile from the bowel, shown by urobilinogen tests or biliary drainage, was important evidence of tumor. If there were both a large, smooth, palpable, nontender gall bladder and signs of complete obstruction, the diagnosis of tumor was practically certain.

An enlarged spleen, ascites, abdominal varices and spider angiomas all pointed toward the medical types of jaundice — acute hepatitis, cirrhoses and so forth — rather than the surgical.

A palpable spleen had definite value in suggesting hepatitis rather than tumor. In the 27 proved cases of tumor of the liver the spleen was not felt in any, whereas it was felt in 10 (27 per cent) of the 38 proved cases of cirrhoses and in many cases of severe acute hepatitis. The roentgen ray sometimes showed an enlarged spleen that was not palpable, and it was sometimes found enlarged at autopsy although not palpable during life. In the 4 cases of cancer that were diagnosed as cirrhosis, the spleen was not palpable. It was enlarged in 7 of the 15 cases of hemolytic anemia of various types.

Ascites was found in both acute and chronic hepatitis and in cancer. In the latter, the specific gravity of the fluid was usually above 1.014 if the peritoneum was involved. It was absent in obstruction due to gallstones.

Spider angiomas of the skin (Eppinger,² Williams and Snell³ and Patek et al.⁴) were found only in well-developed cirrhosis. They were the size of a nickel or dime and consisted of a group of fine arteries radiating from a common center. Pulsation was easily seen on pressure with a glass slide. The angiomas appeared only in the part of the body drained by the superior vena cava — that is, the face, neck, shoulders, chest and arms.

Biopsy of available lymph nodes was at times extremely useful.

Peritoneoscopy^{5,12} is a valuable method of diagnosis that had only a limited use in this series. Its chief value in jaundice is the discovery of cancer or cirrhosis by vision or biopsy. The risk of biopsy is small when it is done with the electrocautery after using vitamin K. In a small number of cases the method fails because of adhesions.

The so-called "liver odor" (fœtor hepaticus⁷), which is marked only in acute necrosis, had a vaguely suggestive value in diagnosis.

LABORATORY TESTS

Most liver-function tests were at their best in judging the degree of damage and surgical risk and in following progress rather than in aiding differential diagnosis, but with serial tests the course of changes of the liver function had some value in diagnosis; for example, in cancer it did not clear up, in complete obstruction it became worse, and in acute, toxic and infectious hepatitis and in cirrhoses — except in very severe cases or in the late stages — it improved.

The depth of jaundice judged by the icteric index gave little or no help in single cases in deciding between obstructive and acute hepatocellular jaundice. There was a wide range, and the averages were close. In 100 cases, the icteric index was as shown in Table 2. The jaundice was often slight and

TABLE 2. Maximum Range and Averages of Icteric Index.

DIAGNOSIS	NO. OF CASES	RANGE OF MAXIMUM	AVERAGE MAXIMUM
Acute hepatitis:			
Infectious	17	22-250	102
Toxic	17	50-200	118
Complete obstruction	31	65-200	116
Cirrhosis and partial obstruction	35	10-225	59
Total	100		

chronic in cases of familial hemolytic anemia. The qualitative van den Bergh test, by indirect and direct reaction, also helped to distinguish hemolytic jaundice from other types. This had only limited clinical value, as already explained. The tint of the jaundice — orange, greenish, bronze and so forth — had little value in distinguishing the obstructive from the hepatocellular type.

The test for urobilinogen in the urine had more diagnostic value than did other tests because it depends on the metabolism of the liver and also on the presence of bile in the bowel. Continued complete absence for two weeks or more strongly suggested complete obstruction of the bile ducts. The urobilinogen in the urine was almost always decidedly increased at some period in the course of acute hepatocellular disease. This test was unsatisfactory in the differentiation of partial obstruction — stone, stricture and cholangitis — and chronic cellular damage.

Bilirubin in the urine usually accompanied an increased icteric index in the blood in all types of jaundice except that due to hemolytic (acholuric) anemia. This absence of biliuria in well-marked icterus was suggestive but was a minor factor in the diagnosis of hemolytic anemia compared with the blood examination and other clinical data. The history, anemia, icterus, splenomegaly, small spherocytes, increased fragility of the red cells, reticulocytes, lack of bilirubin in the urine (usually), excess of bile pigment in the feces, and an indirect van den Bergh reaction in the blood were distinctive. The presence of bile in the urine did not rule out hemolytic anemia, since in some cases there was combined liver damage. Abundant bilirubin in the urine was found in 5 of 14 cases in which hemolytic anemia was combined with cirrhosis, gallstones or passive congestion of the liver.

Many attempts to diagnose obstructive from hepatocellular jaundice have been made by the use of various determinations, such as the total blood cholesterol and cholesterol ester, the blood prothrombin levels and their response to vitamin K,

galactose and glucose tolerance tests, hippuric acid excretion, serum phosphatase levels and cephalin flocculation tests.* There is a fundamental difficulty in this differential diagnosis; in hepatocellular damage — acute and chronic hepatitis — both metabolic and excretion tests are below normal, usually far below, whereas in pure external obstruction in the early stages the tests are normal or close to it, but in later stages of obstruction the lobular cells also become damaged and the tests closely resemble those of the hepatocellular group.

The total blood cholesterol was usually increased in obstructive jaundice. The prothrombin test proved an important measure of the bleeding tendency, and a low test that did not respond to vitamin K gave a bad prognosis, but the cholesterol ester levels and prothrombin tests† had only limited value in differential diagnosis. The sole diagnostic point noted in the prothrombin test was that the percentage was much more likely to rise rapidly to normal after treatment with vitamin K in obstructive jaundice and healing acute hepatitis than in chronic hepatitis (cirrheses).

Other tests that are extremely sensitive, such as the bromsulfalein and hippuric acid excretion tests, were positive in all types of liver damage and had no differential value. The bromsulfalein test was used only when jaundice was slight or absent. Occasional high retention with a low icteric index was an important sign of liver damage without indicating the kind.

The presence of bile pigment in the stools is important in estimating biliary obstruction. No test was better than a rough estimate of color with the eye except the elaborate Watson test for urobilinogen; a simplified Sparkman⁸ test also gave a rough estimate. The disappearance of urobilinogen from the urine was a useful guide to lack of bile pigment in the feces. A series of tests, done daily if desired, is far simpler than medical biliary drainage. A period with acholic stools often occurred in acute liver necrosis, but this rarely lasted more than a week — in exceptional cases two or three weeks.

Early tests for urinary diastase had great value in the diagnosis of acute pancreatitis as a cause of jaundice.

A change in the serum proteins, reduction of the serum albumin (normal about 4.5 gm. per 100 cc.) and lowering or reversal of the albumin-globulin ratio (normal about 2.0) were found in nearly all cases of well-marked disease of the liver and seemed to run parallel to the extent of liver damage. This change may be looked on as an index of liver failure and is highly valuable in the prognosis of chronic liver disease, as well shown by Post and Patek,⁹ but has little or no value in single cases in diagnosing the type of disease — whether acute or

*The cephalin flocculation test⁶ was used in only a small number of recent cases.
†Quick's⁷ one-stage method for prothrombin was used.

chronic hepatitis, cancer of the liver or external obstruction. This is clearly shown in Table 3.

The range of the serum albumin and globulin levels and of the albumin-globulin ratio was similar in the four groups of cases, and the values in single cases apparently depended on the severity of the

TABLE 3 Serum Protein Values in 50 Consecutive Cases

DIAGNOSIS	No of Cases	SERUM ALBUMIN gm/100 cc	SERUM GLOBULIN gm/100 cc	ALBUMIN GLOBULIN RATIO	AVERAGE ALBUMIN GLOBULIN RATIO
External obstruction (gallstone or cancer)	11	15-5.2	19-2.7	0.3-1.3	1.0
Acute hepatitis	11	17-4.7	18-4.4	0.6-2.2	1.4
Cirrhosis	22	15-4.5	21-6.4	0.3-1.6	0.8
Carcinoma of liver	6	14-3.2	24-4.8	0.4-1.2	0.6
Total	50				

illness rather than on the type of disease. All the cancers of the liver were fatal, as were 20 of the 22 cirrhotics, 6 of the 11 external obstructions and 5 of the 11 cases of acute hepatitis.

A positive blood serologic reaction in jaundiced patients does not usually indicate syphilis of the liver. Hepatic cirrhosis and syphilis of the liver are often associated in the literature. In the present series, of 38 cases of cirrhosis with jaundice that came to autopsy there were 7 cases (18 per cent) with a positive Kahn or Hinton reaction but no evidence of syphilis of the liver. In 13,219 general autopsies at the Boston City Hospital between 1928 and 1937 there were 487 cases of cirrhosis of the liver and only 18 cases of acquired syphilis of the liver,* making the percentage of syphilis of the liver 3.7 per cent among the cirrhotics and only 0.14 per cent in the total group. McCrae's¹⁰ statement that syphilis of the liver should be considered in every case of hepatic disease in which the diagnosis is obscure probably applies to the pre-Wassermann days, chiefly covered by his figures, when only 1 case in 7 was recognized clinically. This is at present evidently a rare disease.

Since the only known case of syphilis of the liver in this series showed a negative Hinton reaction and all the other cases with positive Hinton reactions that came to autopsy or operation showed no syphilis of the liver, it cannot be said that the blood serologic test was of much help in this diagnosis. In the last ten to twenty years, most jaundice in syphilitic patients has been due to toxic hepatitis following the use of arsenic in treatment.

The roentgen-ray examination often detected disease of the gall bladder or the primary source of a cancer of the liver, and the discovery of early esophageal varices occasionally aided the diagnosis of cirrhosis before other signs were clear. The Graham test cannot be relied on during an attack of jaundice, when the liver function is usually low and the dye is poorly excreted; the test should if possible be made between attacks of jaundice. Biliary

drainage was not extensively used on account of the time required, but it has special value when there is too much jaundice — and too poor liver function — for a Graham test.

No laboratory test was diagnostic without the clinical background. Improved diagnosis with the addition of laboratory tests was sometimes due not wholly to the tests but partly to more intense study of cases and added clinical experience. At the present time especially, tests with a simple technic easily available to the practitioner or small hospital have the preference. For a fuller discussion of liver-function tests and laboratory data, the reader should consult recent papers on this subject.¹²⁻¹⁷

The discovery of primary cancer of the liver, which develops chiefly in cirrhosis, is difficult by any method. The clinical pictures of late hepatic cirrhosis and primary cancer (hepatoma) are closely similar — namely, gastrointestinal symptoms, discomfort or pain in the right upper quadrant, weakness, loss of weight, hematemesis, fever, jaundice, ascites, anemia, enlarged liver, positive roentgen-ray examination and low liver function. There seems little or no possibility of succeeding in this differential diagnosis unless there is an external nodule or nodules in the liver that can be palpated or discovered on its surface by the roentgen ray or peritoneoscope, or unless there are metastases.

During the last six years we have seen 2 proved cases of primary cancer of the liver in patients with cirrhosis. In one, that of a man of sixty-four with jaundice, the evidence pointed equally to cirrhosis and to massive cancer of the liver from an unknown source, and both diagnoses were given equal value. In the other, that of a Chinese of sixty-six, a diagnosis of hepatic cirrhosis and cancer of the esophagus, with metastases to the lung, pleura, lymph nodes and bones, was made. At autopsy, cirrhosis, primary cancer of the liver, epidermoid cancer of the esophagus and a teratoma of the lung with adenocarcinoma were found.

SUMMARY AND CONCLUSIONS

The course of the jaundice often aids diagnosis, and since cases of jaundice are rarely emergencies, a short study period is useful. Tests of liver function should be repeated in series.

A short course of moderate to severe jaundice with marked loss of liver function was due oftener to hepatocellular damage than to obstruction. Acute deep jaundice with brown stools was almost always of the hepatocellular type.

The value of the depth of the jaundice, the size of the liver and a palpable gall bladder were often overestimated in differential diagnosis. The icteric index in acute hepatitis and complete external biliary obstruction were much alike. An enlarged liver was a valuable sign of hepatic disease, but was of such common occurrence that it gave little help in deciding the kind. The gall bladder could be

*All these syphilitic livers in adults showed more or less fibrosis and were classified as syphilitic cirrhosis.

palpated in only one third of the cases of malignant obstruction of the common duct; complete absence of bile from the stools was far more frequent and constituted important evidence of obstructive tumor. Complete obstruction due to cancer almost never improved.

The spleen was not palpable in any case with tumor of the liver, but was felt in 27 per cent of the cirrhotic cases. Spider angiomas were found only in portal cirrhosis. Fever and leukocytosis in late cancer sometimes simulated cholangitis and liver abscess. In deep jaundice an absence of bilirubin in the urine suggested hemolytic anemia, a diagnosis that was readily confirmed by other tests.

The test for urobilinogen in the urine often gave direct help in diagnosis of complete obstruction from hepatocellular damage and from partial obstruction. Other tests, such as hippuric acid and bromsulphalein excretion, were positive in all types of liver disease and had no differential value. Some tests that are useful in prognosis and for which differential value has also been claimed, such as the amount of cholesterol ester in the blood, the prothrombin level and its response to vitamin K and changes in the levels of serum proteins and in the albumin-globulin ratio, had little or no differential value.

In the diagnosis of acute pancreatitis with jaundice, early tests for diastase in the urine proved simple and highly valuable.

Positive Hinton, Kahn or Wassermann reactions in jaundiced patients usually did not indicate syphilis of the liver.

The roentgen ray often detected gall-bladder disease, the primary source of a cancer of the liver and esophageal varices. During deep jaundice the

Graham test had little value on account of poor excretion of the dye by the liver.

I am indebted to Dr. Emmanuel Deutsch for many liver function tests done in the Surgical Research Laboratory Boston City Hospital.

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THE THERAPEUTIC VALUE OF TWO NEW SULFONAMIDE COMPOUNDS, SUCCINYL-SULFATHIAZOLE AND PHTHALYLSULFATHIAZOLE, IN EXPERIMENTAL TRICHINOSIS*

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DESPITE the wide and successful use of sulfonamide compounds in the treatment of bacterial infections, they have not been found to be particularly promising as therapeutic agents in diseases caused by animal parasites. It must be admitted, however, that present knowledge of the value of these drugs in the treatment of parasitic diseases has scarcely advanced beyond the experimental stage. It has been shown that sulfanilamide is a complete sterilizing agent against the malarial parasite *Plasmodium knowlesi* in rhesus monkeys, but it is not usually effective in human malaria due to *P. vivax*,¹ whereas both promin and sulfadiazine are definitely active against the three common species of human malaria.² Encouraging results have been obtained with sulfaguandine used to combat coccidiosis in chicks,³ lambs⁴ and calves.⁵ Critical tests with sulfanilamide derivatives against amebic infections have not been performed. Fairley,⁶ however, noted that amebic ulcers heal during sulfaguandine therapy, but that they relapse after cessation of treatment. Keil⁷ observed no effect on the numbers of bancroftian microfilariae in the blood of 9 lepers treated with Prontosil. McCoy⁸ found sulfanilamide to be entirely ineffective in the treatment of trichinosis in rats.

At the present time there is no specific treatment for trichinosis. Constant world-wide search has utterly failed to find an anthelmintic that will remove the adult worms from the intestinal tract or destroy the larvae in the blood stream and muscles.

The physical properties of two new sulfonamide compounds, succinylsulfathiazole (sulfasuxidine) and phthalylsulfathiazole (sulfathalidine), are such that they suggest possible anthelmintic activity. Both are sparingly absorbed from the gastrointestinal tract, and a high concentration can be maintained in the diseased intestine without causing untoward toxic manifestations.^{9, 10} They have extremely high bacteriostatic properties, their action being essentially limited to the local effect on the contents of the gastrointestinal canal.¹¹ It therefore seemed important to determine whether these drugs also had anthelmintic properties in trichinosis, especially against the intestinal stages of the parasite.

The tests with both drugs were similar. A single experiment was made for each drug in the following manner:

Five guinea pigs each weighing approximately 260 gm., were forcibly fed approximately 3000 infective *Trichinella*

larvae. Two days later at which time the worms had approached sexual activity in the small intestine,¹² treatment of 3 of the animals was started. Food was withheld for fifteen hours prior to treatment but was replaced again after the first administration of the drugs. Each of the 3 treated guinea pigs received by a stomach tube at 9 a.m., noon, 3 p.m. and 6 p.m., on two consecutive days, 0.5 gm. of one or the other of the drugs† suspended in 1 cc. of water. Three days after treatment was begun, or five days after the infective feeding, 1 of the untreated and 2 of the treated animals were sacrificed and their intestines examined for adult parasites. The remaining animals 1 untreated and 1 treated were sacrificed thirty days after receiving the infective larvae. Direct microscopic examinations for encapsulated trichinae were made on bits of masseter and diaphragm muscles pressed between two glass slides.

The dosage used was arbitrarily determined. Poth and Knotts⁹ fed dogs 1 gm. of succinylsulfathiazole per kilogram of body weight daily in six divided doses for ninety-five days without the development of toxic manifestations. A marked lowering of the number of coliform bacteria occurred after twenty-four hours and persisted throughout the experiment. According to Poth and Ross¹⁰ phthalylsulfathiazole has two to four times the bacteriostatic activity of succinylsulfathiazole. It is believed, therefore, that our dosage, approximately 8 gm. per kilogram a day for two consecutive days, was adequate to demonstrate any trichinocidal effect of these drugs.

The results obtained from both drugs were essentially the same. No deaths occurred among the untreated and treated animals. The untreated animals showed no signs of trichinosis. Loss of appetite, loss of weight and transient soft stools were characteristic developments among all the treated animals. These were believed to be toxic manifestations of the drugs.

Adult worms were equally numerous in the intestines of both untreated and treated animals. The worms were alive and normally active, and the females were gravid with living embryos. Both animals sacrificed thirty days after infection appeared equally parasitized with encapsulated trichinae. Thus, no evidence was obtained that either succinylsulfathiazole or phthalylsulfathiazole has any value in the treatment of trichinosis.

SUMMARY

The effect of two new sulfonamide compounds, succinylsulfathiazole and phthalylsulfathiazole, in the treatment of experimental trichinosis is described.

The experiment showed that neither succinylsulfathiazole nor phthalylsulfathiazole is of any value in the treatment of trichinosis.

*The compounds for this test were supplied by Sharp and Dohme Incorporated Philadelphia.

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MEDICAL PROGRESS

MALARIA IN MASSACHUSETTS

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MALARIA has been known to exist in Massachusetts from the earliest colonial times. Unfortunately, the malarial parasite and the transmission of malaria by mosquitoes were not discovered until the latter part of the nineteenth century. Consequently, it is difficult to determine the magnitude of the malaria problem in Massachusetts previous to that time, since many clinical entities were confused because of the lack of diagnostic refinements. There is, however, a certain amount of information concerning the prevalence of intermittent fever, ague, bilious fever, malignant fever, pond fever or mortal fever, as malaria was variously called in earlier times. Perhaps the completest early account of malaria in Massachusetts is to be found in the Boylston Prize Dissertations of 1836, in which Oliver Wendell Holmes¹ presented a paper entitled "Indigenous Intermittent Fever in New England." This paper was based on a review of the previous writings on the subject and personal communications from physicians.

From his search among the early writings on medical history in New England, Holmes concluded that intermittent fever existed in at least several places in New England but that the records of its existence in the literature were scanty and inaccurate. The second portion of his paper consists of replies to inquiries that he had sent to physicians throughout New England. This method of surveying the malaria situation was more fruitful, and Holmes gathered a large amount of disconnected information on the prevalence of intermittent fever in this region. In many cases, there can be no doubt that the disease concerned was malaria. In some accounts it is apparent that it was tertian malaria. Many of these outbreaks of intermittent fever were due to movements of population, concerned mainly with new construction, in particular dams, and the drainage of marshes.

The first epidemic of malaria in Massachusetts took place at the close of the eighteenth century and existed in the western portions of both Massachusetts and Connecticut along the Housatonic River basin. The second epidemic appeared from 1828 to 1832 in Connecticut along the shore of Long Island Sound, and slowly moved in a northeasterly direction, eventually reaching western Massachusetts. No appreciable number of cases were reported in Massachusetts after 1836. The third epidemic began in New Haven about 1850 and remained within the vicinity of Long Island Sound for the ensuing fourteen years. In 1865, the disease began to spread northward, and it first appeared in Massachusetts in Springfield in 1870. During the ensuing nine years malaria spread in a northerly direction up the Housatonic and Connecticut rivers.

In 1880, Adams² made a survey of the malaria situation since 1836, by means of correspondence, personal observation and inquiry. By this means, the existence of malaria was ascertained in forty-eight cities and towns, and its absence in one hundred and sixty-three. There were no replies from one hundred and twenty-eight towns, but the author states that replies were received from almost every place of any size or importance.

In 1884, Chapin³ wrote a paper entitled "The Origin and Progress of the Malarial Fever Now Prevalent in New England." He gave data on the occurrence of malaria in Massachusetts in 1881, 1882 and 1883. In 1881, malaria reappeared in the towns where it had appeared the previous year, with an increase in the number of cases and in mortality. Chapin remarks that the term "malaria" was beginning to replace the term "intermittent fever" in Massachusetts. In 1882, malarial diseases continued in the same towns, with an increase in deaths. In 1883, there was a general decrease in the number of cases, although nothing had been done in the way of sanitation to secure the result. Chapin judged

*Commissioner, Massachusetts Department of Public Health; lecturer in public health practice, Harvard School of Public Health.

that the decrease in malaria was entirely dependent on natural causes.

In 1889, Cook⁴ made a study of malaria in eastern Massachusetts. He concluded that prior to the previous four years malaria as an epidemic disease was unknown in eastern Massachusetts. The then prevailing epidemic was in reality a continuation of the epidemic of the seventies that had occurred in the western part of Massachusetts. Since the summer of 1885 at least twenty-two cities and towns in the counties of Middlesex, Norfolk and Worcester, not counting those where there had been sporadic cases,

concluded that whereas typhoid fever and other diseases had possibly complicated the picture, malaria did exist in the various epidemics that had been described by the several writers. He decided that the origins of the various epidemics could be discovered only by a careful study of contemporary local history, with special reference to movements of population and modes of living. He contended that even without any appreciable influx of immigrants from countries in which malaria was prevalent, the southern states could at any time have furnished a sufficient quota of malaria carriers to start an

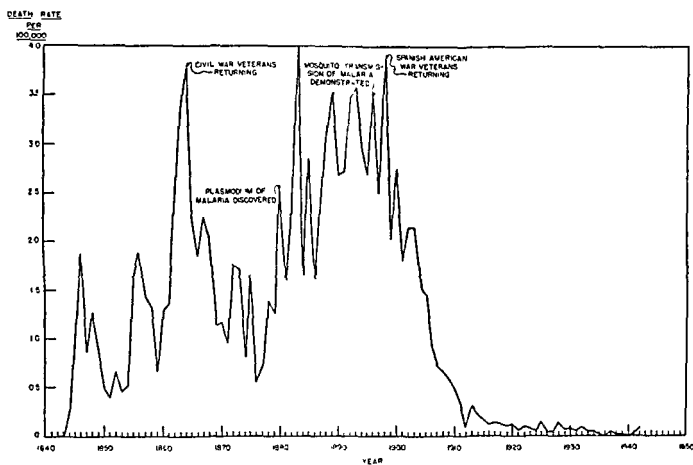


FIGURE 1. Malarial Death Rate in Massachusetts.

reported the prevalence of malaria. These towns were distributed along the Charles, Sudbury and Blackstone rivers.

In 1903, Smith⁵ published in the *Boston Medical and Surgical Journal* a series of articles entitled "The Sources, Favoring Conditions and Prophylaxis of Malaria in Temperate Climates, with Special Reference to Massachusetts." Since the relation of mosquitoes to malaria as carriers was established by that time, and since the malarial parasite had been discovered, the diagnosis of malaria and the study of its spread are more reliable in the work of Smith than in that of the earlier writers mentioned. Smith made a survey of mosquitoes in Massachusetts and found *Anopheles maculipennis*—which was apparently confused with *Anoph. quadrimaculatus*—to be the commonest mosquito of any of the anophelines. He discussed the life, habits and breeding places of this mosquito, together with those conditions that favor mosquito breeding. Finally, he reviewed the history of malaria in Massachusetts and its status at the time in the light of the biological discoveries mentioned above. Smith

epidemic under favorable local conditions. According to this author, the last invasion of New England by malaria, which began, roughly, in the sixth decade of the nineteenth century and extended through the first decade of the twentieth century, was largely due "to the great material development which found expression in many new public and private enterprises, such as the construction of railroad beds and highways, the introduction of public water supplies and sewerage plants, the building of mills and the drainage, filling and grading of suburban territory and the like." In connection with these enterprises, the sources of infection during the preceding thirty years he regarded as coming from the Italian, Hungarian and other immigrants from endemic foci and the contingent of Negro laborers from the southern states.

In 1926, Quinn⁶ made a study of malaria in New England by mailing questionnaires to the health department of each of the New England states, to sixty-five representative cities and towns and to a number of hospitals. He pointed out that anophelines existed in all parts of New England below

a 2000-foot altitude, but that the mosquito is merely the connecting link between the malarial patient and the noninfected person. The plasmodium of malaria was brought in by immigrants from malarious sections of the world. Rigorous winters, cool summers and mosquito-control measures, however, together with quinine medication, prevented the completion of the necessary chain of malarial patient, mosquito and noninfected person. The author reported the existence of an epidemic focus of malaria in Manchester, New Hampshire,

malaria began to manifest itself in 1880 and continued until 1898, when the deaths again began to decrease. This second wave of deaths from malaria, as recorded in these reports, was caused by three factors. The first was the epidemic of malaria in Massachusetts that has already been discussed. The second was the effect of the Spanish-American War on this disease, which was seen in the peak of 1898; during this year many soldiers returned to Massachusetts after contracting the disease in Florida or Cuba. The third comprised better diagnostic facilities, in part due to the increased knowledge concerning malaria. The plasmodium was demonstrated during this period, and the mosquito transmission of malaria was proved, as well as the mosquito transmission of yellow fever.

With the turn of the twentieth century, deaths from malaria began to decrease rapidly, reaching a new low in the late 1920's. These deaths have averaged 1.8 per annum during the last ten years, indicating a case fatality of 8.9 per cent on a basis of the reported cases over the same period.

Morbidity statistics. It was not until 1914, however, that malaria itself was made reportable, when the Massachusetts Department of Public Health declared it to be a disease dangerous to the public health. At that time malaria was endemic in several places within Massachusetts.

In 1915, the first year for which the figures are complete, the reported incidence of malaria was the greatest. Since then the disease has a continued decreasing trend (Fig. 2) and reached an extremely low level in the five years immediately preceding the present war. Since 1941, however, there has been a continuous increase in the number of reported cases. Malaria was prevalent in Boston from 1915 to 1928. Most of these cases were in sailors who had acquired the infection in the tropics and were hospitalized in this city. Some of the cases, however, were connected with a new sewer project where Italian labor was employed. The high incidence of malaria in Chelsea from 1928 to 1935 is explained by the fact that the United States Marine Hospital was located there and received many sailors from foreign countries. The epidemic of 1918 in Ayer was due to the presence of large numbers of troops at Camp Devens some of whom were from the South.

In all there are three areas in Massachusetts where malaria has existed within the last twenty-five years. In each instance the disease ceased to be endemic in the area about twenty years ago. These areas are as follows:

The Charles River drainage area. The disease was prevalent here from 1915 to 1921. It apparently occurred first in Natick and Newton and spread to the neighboring communities of Dedham, Framingham and Wellesley. The town of Dedham has a large Italian colony. This is also true of Milford, in the upper part of the Charles River area, where malaria was prevalent from 1919 to 1924. Older residents of this part of the Charles River basin state that malaria was common in their childhood during the first

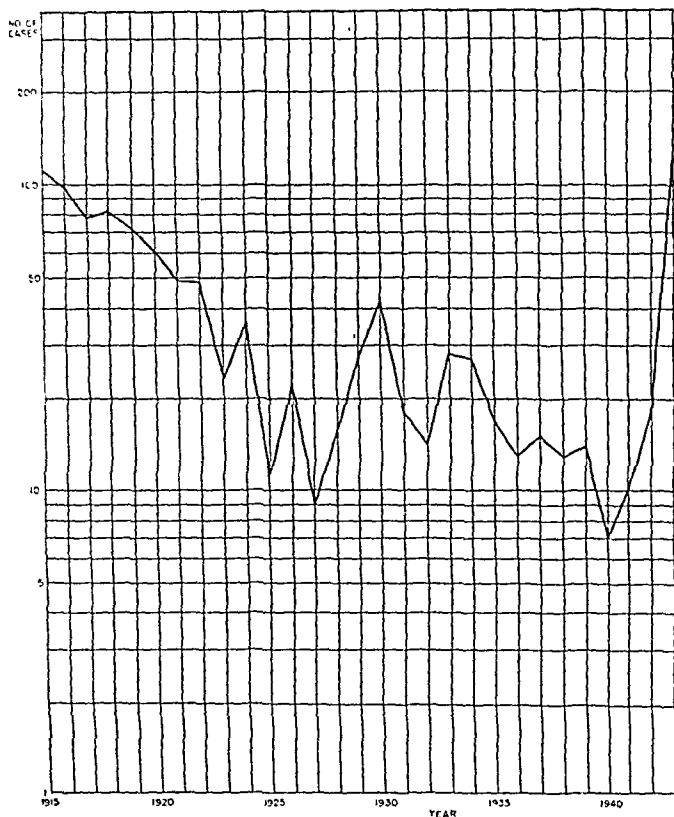


FIGURE 2. Reported Cases of Malaria in Massachusetts.

and in Connecticut, and also the incidence of malaria in several communities in Massachusetts, totaling 445 cases during the period 1917-1924.

Present Status of Malaria

Mortality statistics. Deaths from malaria were made reportable as early as 1842. At first these were reported as "intermittent fever" and "remittent fever"; from 1855 to 1900 the terminology was changed to "ague" and "remittent fever," and from 1901 to 1911 to "intermittent fever" and "malarial cachexia." Finally, since 1912 the disease has been reported as "malaria."

A study of these reported deaths (Fig. 1) reveals that there have been several peaks during the last hundred years. The first peak was reached in 1864 and was associated with an importation of the disease in Union soldiers who returned from the Civil War. A second increase in deaths due to

decade of the twentieth century. It is not unlikely that it may have been a hang-over from the epidemic wave of the last quarter of the nineteenth century. Probably there have been many more cases of malaria in this region than were reported.

The Blackstone River basin. Malaria was endemic in this region from 1915 to 1921, particularly in the towns of Uxbridge, Douglas and Northbridge.

The Taunton River basin. Here malaria persisted from 1915 to 1922. The same etiologic factors were responsible for disease in these regions as in the Charles River drainage area.

Malaria acquired in Massachusetts. The Massachusetts cases can be divided into two major groups, intrastate infections and out-of-state infections

setts. Doubtless, these infections were acquired from gametocyte carriers who infected the mosquitoes in the vicinity of the victim.

During the last fourteen years, 6 patients have acquired malaria as a result of transfusions. To prevent a repetition of this unfortunate accident and the similar transference of syphilis, under a law⁷ passed by the Massachusetts Legislature in 1938, the Department of Public Health made regulations relative to transfusions. On April 10, 1939, these regulations⁸ became effective. The regulation reads, "No person shall introduce the blood, or any

TABLE 1. *Reported Cases of Malaria in Massachusetts.*

TYPE	1930	1931	1932	1933	1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	TOTALS
Intrastate:															
Natural	3	1	2	2	0	0	1	0	3	0	0	0	0	0	11
Therapeutic	5	0	0	0	5	1	2	3	2	5	0	6	1	0	49
Transfusion	0	0	0	0	2	0	0	0	0	1	0	2	0	0	6
Other	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Totals	9	6	3	14	7	1	4	3	5	6	0	8	1	0	67
Out-of-state:															
Civilian	13	6	2	12	10	13	8	9	7	5	5	1	2	3	96
United States Marine Hospital	20	5	6	2	6	2	0	1	0	0	0	1	0	0	43
Military	0	0	1	0	0	0	0	0	0	0	0	0	13	113	127
Totals	33	11	9	14	16	15	8	10	7	5	5	2	15	116	266
Miscellaneous	0	1	2	0	4	1	1	2	1	3	2*	0	2	5	24
Grand totals	42	18	14	28	27	17	13	15	13	14	7	10	18	121	357

*One congenital

(Table 1). The former group represents but a small proportion of the total, less than 25 per cent of the reported cases being acquired within the boundaries

TABLE 2. *Cases of Natural Infection with Malaria in Massachusetts.*

YEAR	NAME	AGE yr.	SEX	CITY OR TOWN
1930	M B	50	F	Uxbridge
	R P	38	F	Springfield
1931	M W	60	F	Newton
1932	W R	40	M	Boston
1933	C W	42	M	Attol
	H O	28	F	Westboro
1936	A T	23	M	Acton
1938	T F	50	F	Natick
	B Z	2/12	?	Worcester
	K M	2	M	Haverhill
	D D	19	F	Boston

of the Commonwealth. Moreover, most of these were cases induced in the treatment of syphilis of the central nervous system. Since 1930, a total of fourteen years, there have been only 11 cases that were probably naturally acquired within the Commonwealth. These patients were presumably bitten by Anopheles mosquitoes that were carriers of malaria. These cases were scattered throughout the Commonwealth (Table 2), and there is no evidence that there was any connection between them. In some cases—namely, the two children who acquired the infection during 1938—there were malaria cases in the same or a neighboring household. The source of the infection in the other 9 cases, however, has not been established. Malaria is certainly not epidemic in this state, nor can it be said to be endemic. The number of naturally infected cases averages less than one a year, and the disease can therefore be called a rare phenomenon in Massachu-

setts. Of the cases of malaria reported in Massachusetts since 1930, over 75 per cent were acquired beyond the limits of the Commonwealth. During peacetime, these patients were civilians who had traveled in the southern United States or had visited tropical or subtropical countries. The largest group of out-of-state cases was reported by the United States Marine Hospital among merchant seamen who stopped at African ports. Since 1941, however, a new and important importation of cases has occurred. These are servicemen of the armed forces and prisoners of war. The vast majority of cases (95 per cent) reported in 1943 were from military organizations or among servicemen who were home on leave and developed symptoms of malaria after their arrival in the State.

Vectors of Malaria

During the summer of 1939, the Massachusetts Department of Public Health conducted, in cooperation with the Work Projects Administration, a survey of mosquitoes that were vectors of disease. This investigation was made on the recommendation of Brigadier General J. S. Simmons, then assistant surgeon of the First Service Command, United States Army, following an outbreak of equine encephalomyelitis involving about 300 horses and

34 human beings.^{9, 10} The survey determined the seasonal and geographical distribution of the fifty-six species of mosquitoes in Massachusetts, collected data on their life habits, and determined the epidemiologic importance of the various species. The conclusions reached were based on 49,084 collections comprising 278,557 specimens.¹¹ These mosquitoes and the accompanying data were gathered

house mosquito, and *Mansonia perturbans*, which is most numerous in early summer. It has been collected in all parts of the Commonwealth and represents about one fourth of all Anopheles. Three other anophelines, *Anoph. maculipennis*, *Anoph. walkeri* and *Anoph. crucians*, transmit malaria and act as important vectors in other parts of the world. In Massachusetts all three of these are rare and

TABLE 3. Genera of Massachusetts Mosquitoes, With Percentages of Adults and Larvae (1939).

GENUS	ADULTS		LARVAE		NO OF SPECIMENS	RELATIVE INCIDENCE %
	NO	PERCENTAGE	NO	PERCENTAGE		
Aedes	8,409	46.4	9,733	53.6	18,142	6.6
Anopheles	1,260	3.8	31,728	96.2	32,988	11.9
Culex	7,443	3.5	206,206	96.5	213,649	77.3
Mansonia	6,663	91.1	649	8.9	7,312	2.6
Psorophora	4	44.4	5	55.6	9	0.0
Theobaldia	90	4.3	2,004	95.7	2,094	0.8
Uranotaenia	14	6	2,312	99.4	2,326	0.8
Wyeomyia	9	36.0	16	64.0	25	0.0
Orthopodomyia	0	0.0	3	100.0	3	0.0
Totals	23,892	8.6	252,656	91.4	276,548	

by one hundred WPA collectors and numerous volunteers enrolled with the co-operation of various federal and state institutions, local boards of health and other organizations.

Only two of the nine genera of biting mosquitoes of Massachusetts are known to contain species that may act as vectors of human disease. The statistical importance of these genera varies greatly (Table 3). Culex mosquitoes comprise 77 per cent of all mosquitoes and do not transmit any known disease of

epidemiologically unimportant in the transmission of malaria. *Anoph. punctipennis*, although a possible vector of malaria, because of its large numbers may play a role as a vector. It is distributed throughout the Commonwealth, is about three times as numerous as *Anoph. quadrimaculatus*, and breeds almost any type of water collection, clear or foul, large or small.

From these observations, the possibility of an outbreak of malaria can be visualized. The vectors

TABLE 4. Anopheles of Massachusetts, 1939.

SPECIES	ADULTS		LARVAE		NO OF SPECIMENS	RELATIVE INCIDENCE %
	NO	PERCENTAGE	NO	PERCENTAGE		
crucians	0	0.0	20	100.0	20	0.1
maculipennis	30	21.6	109	78.4	139	0.4
punctipennis	302	1.5	20,442	98.5	20,744	62.9
quadrimaculatus	782	10.3	6,808	89.7	7,590	23.0
walkeri	78	49.7	79	50.3	157	0.5
Unidentified*	68	1.6	4,270	98.4	4,338	13.1
Totals	1260	5.8	31,728	96.2	32,988	

*Too small or too damaged for identification

man in Massachusetts. Aedes represent 7 per cent of the mosquitoes, and of the twenty-one species in this genus, six have been shown to transmit the Eastern strain of equine encephalomyelitis in the laboratory.^{11, 12} All the other genera except Anopheles comprise less than 5 per cent of the mosquitoes, and none of them are vectors of the disease. The genus Anopheles, comprising 12 per cent of the mosquitoes, is responsible for the transmission of malaria. In Massachusetts this genus is represented by five species, one of which, previous to the survey, was not known to inhabit Massachusetts (Table 4).

Anoph. quadrimaculatus is the most important vector of malaria in Massachusetts. It is an ubiquitous breeder but prefers large, clear bodies of water. Most numerous in July and August, it is a vicious biter and enters buildings oftener than any other mosquitoes except *Culex pipiens*, the common

malaria are present in all parts of Massachusetts. With susceptible persons likewise present, only one additional factor is needed to complete the cycle, namely, gametocyte carriers.

Epidemiology

From the study of malaria in the past and the present status of the disease in Massachusetts, it can be concluded that malaria has existed in this state as an endemic disease for many years in both the eastern and western portions, that it has crept over portions of the Commonwealth in at least three epidemic waves, that it has been practically eradicated from Massachusetts and that, at the present time, it is not a public-health problem. If the absence of malaria from Massachusetts could be depended on, there would be no justification for raising this problem at the present time.

Fortunately, climatic and environmental conditions in Massachusetts are unfavorable for the continued endemicity of malaria. Although there have been epidemic periods in the past, the disease has almost disappeared between these times of high prevalence. Each year, Massachusetts¹³ becomes less favorable for the breeding of *Anopheles* mosquitoes. Ponds are kept clear of vegetation offering protection to the larvae; marshy areas about ponds and streams are gradually filled; and with the building of each new house more land is graded and more mosquito-breeding places are destroyed. These factors, limiting the breeding of vectors, and the excellent screening of houses and the prompt treatment of cases of malaria undoubtedly play important roles in preventing a major outbreak.

Malaria, however, increased to epidemic proportions following the Civil War and the Spanish-American War, when servicemen returned from malarious areas, bringing the infection with them. During World War I, although malaria was prevalent among the troops in southeastern Europe,¹⁴ our forces did comparatively little fighting in areas of endemic malaria. Consequently, as Simmons¹⁵ points out, there was only a slight increase of malaria in the United States Army and this was quite transient. In turn, there was practically no transmission of the disease from the military to the civilian population, and Massachusetts malaria rates were practically unaffected by the war of 1914-1918. Other parts of the world, however, were less fortunate. Malaria returned to plague areas in Europe, from which it had disappeared for years, and Russia experienced the most terrible epidemic of modern times.¹⁴

Malaria and the War

In the present war,¹⁶ the importance of malaria cannot be minimized. The surrender of Bataan can be, at least in part, ascribed to malaria and the lack of quinine. Practically all the South Pacific islands are free from malaria except those between the Equator and latitude 20° S. from New Guinea east to longitude 170° E.¹⁷ Malaya,¹⁸ Burma,¹⁹ India, Africa and the entire Mediterranean basin are rife with malaria.

The Army has taken all possible precautions to control malaria.²⁰ Under battle conditions,²¹ however, exposure to malarious mosquitoes is inevitable, and consequently many soldiers, sailors and marines have acquired the parasites. Geiman²² has reviewed the advances in research and their application to the malaria problems facing the entire world as a result of this war. On the return of these soldiers to the United States and to their homes or to hospitals, there is danger of spreading the disease to civilians. The danger of introducing malaria to Massachusetts,²³ to New York,²⁴ to other parts of the United States²⁵ and to Australia,²⁶ in fact to almost any region where anophelines are known to exist,²⁷ has been pointed out by numerous authors.

Through a program entitled "Malaria Control in War Areas," the United States Public Health Service²⁸ has been conducting a project designed to control breeding of disease-bearing *Anopheles* mosquitoes and to reduce potential malaria transmission in extracantonment zones of military establishments and in essential war industries. Up to 1943, the vast majority of this work was limited to the area south of the Mason and Dixon Line. Recently, as a result of surveys of mosquitoes made in the vicinity of certain military establishments in Massachusetts, the program has extended its activity into New England.²⁹ This organization³⁰ is giving special attention to areas adjacent to Army general hospitals where casualties from malarious areas may be quartered. Some of these hospitals are assisted by active control measures, others are undergoing entomologic surveillance, and in some, surveys have been completed. Similarly, prisoner-of-war camps are being surveyed and in some instances assisted with malaria-control programs. Thus far, only entomologic surveys have been made in and about military establishments in Massachusetts. In several instances, however, control measures have been instituted in military establishments against mosquitoes primarily as pests.

The Massachusetts Department of Public Health and the Reclamation Board³¹ have been co-operating with the armed forces and with the control program of the United States Public Health Service described above in making surveys of the extracantonment areas of military establishments in this state. Thus far, the expenditure of money for mosquito control in Massachusetts has been directed at the nuisance and pest angle and not specifically against vectors of disease. As yet, in Massachusetts, no funds have been expended specifically against the anophelines. Data, however, are being assembled to enable efficient control measures against anophelines as soon as a need for these develop. In one instance the personnel of the Massachusetts Reclamation Board have been active in instructing a large number of troops in mosquito-control measures so that they in turn may become proficient in applying these measures against *Anopheles* when they go abroad into zones where malaria is prevalent.

The reintroduction of malaria into Massachusetts may come from three sources. The first of these is the presence of carriers of the usual strains in large numbers, thereby giving rise to cases in the immediate vicinity. If patients are properly treated and are kept under screens, especially after dusk, this danger can be reduced to a minimum, especially when combined with measures designed to reduce the anophelines below the level necessary for endemicity. Any such outbreak will be temporary and limited in geographical area, since the factors that are responsible for the eradication of malaria are still in operation and will again eradicate the disease. The second source is new species of mosquitoes that are better

vectors, which may be brought by airplanes and ships and thereby enhance the spread of the disease. The classic illustration is the introduction of *Anoph. gambia* from Africa to Brazil and the subsequent epidemic of malaria.^{32, 33} More recently, *Anoph. albimanus* was discovered in an area adjacent to a Florida airport³⁴; since this species is not native to Florida, there is only one explanation for its presence near the airport. Active disinsectization of all airplanes and ships from malarious areas is the only sure safeguard against bringing new vectors into Massachusetts. The third source comprises new species or strains of malarial parasites introduced either by human carriers or by mosquito vectors. Such a plasmodium, if it finds a more efficient vector, may create a serious outbreak.

Malaria Control

Adequate control of malaria must be based on one or more of the following procedures: control of mosquito vectors; protection from the bites of infected mosquitoes; immunization of susceptible persons; removal of sources of infection of mosquito vectors by isolation of cases or treatment of carriers; and prevention of entry of mosquito vectors and possible sources of infection into areas as yet unaffected by the disease.

Mosquito control. Certain conditions are necessary before a mosquito-borne disease can become epidemic or reach a high endemic index. One of these conditions is the existence of a numerical relation between the hosts, vectors and susceptible persons. When this relation is upset by a reduction of the number of vectors, the disease ceases to be epidemic and rapidly declines, either arithmetically or geometrically, depending on the interrelation of many factors. It becomes apparent that a moderate reduction in the number of mosquitoes below the critical level will markedly reduce the prevalence of the disease in an area where there are many immune persons, but in a region with many susceptible persons the reduction below the critical level must be much greater. This concept was developed by Ross,³⁴ who applied it to malaria. Carter³⁵ and Gorgas³⁶ applied it to yellow fever.

The bionomics of mosquitoes³⁷ are such that control measures must be designed to eliminate or control the larvae or the adults. The measures that are most effective in any area depend on the local factors and on the species of mosquitoes concerned. It is impractical and uneconomical to attempt to control all mosquitoes. The control measures must be directed against the species that it is desired to reduce below the critical level. Therefore, in order to ensure effective control measures, it is important to understand the bionomics, breeding habits, seasonal and geographical distribution and identification³⁸ of the species that are concerned with the transmission of the disease. Since local circumstances vary, it is necessary that a mosquito survey³⁹

be made before control measures are introduced into a new area for the purpose of controlling mosquito-borne disease. Even in controlling mosquitoes as a nuisance, it is necessary to determine their bionomics before an economical and efficient nuisance control can be expected.

Protection from mosquitoes. Effective protection from the bites of mosquitoes can be accomplished only under extremely limited conditions, especially in combat.⁴⁰ Screening and avoidance of unnecessary exposure are the most effective methods. Spraying in houses, and out-of-doors, the application of mosquito repellents and the killing of adult mosquitoes are adjuvants. For this method to be completely effective, man would necessarily have to remain behind screens at all times. Since this is practical impossibility,⁴¹ protection against mosquito bites is only partial.

Immunization of susceptible persons. There is specific immunization against malaria. The suppressive treatment with quinine or atabrin is an attempt to destroy or suppress the multiplication of the plasmodium as soon as it is introduced in the blood stream. These drugs merely act as suppressives and not as prophylactics, and are not recommended for residents in Massachusetts. Atabrin⁴² is about as effective as quinine⁴³ in preventing clinical attacks of the disease, and both drugs⁴⁴ being used in combat areas. Plasmoquin⁴⁵ has proved valuable as a suppressive and is not recommended for prophylactic use. The development of a good prophylactic against malaria would be one of medicine's greatest gifts to humanity.

Removal of human sources of infection. Removal of human sources of infection is effective only to a limited extent. Patients with the disease or gametocyte carriers, with the infecting agent in the circulatory blood, may act as foci of infection for vectors, and are usually the foci of outbreaks of disease in new areas. It is therefore sound preventive medicine to isolate these persons in mosquito proof quarters.

Prevention of entry into new areas. Malarial patients entering the country from abroad should be maintained under observation at least three weeks after the stopping of suppressive treatment with atabrin or quinine, since most cases develop symptoms by that time. The patients should receive adequate therapy in screened quarters,⁴² and after discharge from the hospital must be followed in order to detect recurrences adequately. In this way, most of these patients will be rendered non-infectious to mosquitoes and will not act as foci for local outbreaks.

Airplanes must be adequately treated to prevent the importation of infected mosquitoes. With the increase of speed of travel, many planes may transport patients from one continent to another within the incubation period of disease. New quarantine regulations and procedures to protect the Nat-

from malaria and other infectious disease must be developed and implemented in the near future

CONCLUSION

Three factors are necessary for the continued existence of malaria in any area ⁴⁶ These are gametocyte carriers, which are entering Massachusetts in increasingly larger numbers, chiefly as servicemen and prisoners of war, certain species of Anopheles mosquitoes that can transmit the disease, and susceptible persons who can be infected

The prevention of malaria in the future and its control in Massachusetts can be achieved by two methods. The first is the prevention of the infection of Massachusetts mosquitoes by gametocyte carriers who may act as the source of the epidemic, through adequate treatment and screening of patients. This method, however, is not entirely dependable, since it is impossible to ascertain which asymptomatic persons are gametocyte carriers, and tests that could determine the presence of gametocytes in the blood of all persons who enter the Commonwealth are both difficult to perform and enforce.

The second and most practical method of controlling malaria is by an attack on the mosquito vectors. Such an attack, however, must be based on accurate knowledge of the distribution of the vectors. The recording of data on the seasonal prevalence and geographic distribution of the mosquito vectors of malaria is one of the accomplishments of the mosquito survey,⁴⁷ conducted by the Massachusetts Department of Public Health in 1939. The United States Public Health Service,³⁷ assisted by state and military agencies, is making detailed surveys of extracantonment areas of military establishments where malaria patients are likely to be hospitalized.

Should there be any evidence of spread, mosquito-control measures must be directed against those mosquitoes that are carriers of disease, the number of vectors thus being lowered to a number that is insufficient either to maintain the existence of malaria or to permit its introduction.

It is unlikely that malaria will again become endemic in Massachusetts as a result of this war. Sporadic cases may occur, but any larger outbreak will probably be short-lived and geographically limited. Under proper safeguards, Massachusetts and most of New England are relatively safe from any extensive epidemic of malaria.

REFERENCES

- malaria and other infectious disease must be developed and implemented in the near future
- ### CONCLUSION
- Three factors are necessary for the continued existence of malaria in any area.⁴⁶ These are gametocyte carriers, which are entering Massachusetts in increasingly larger numbers, chiefly as servicemen and prisoners of war, certain species of Anopheles mosquitoes that can transmit the disease, and susceptible persons who can be infected.
- The prevention of malaria in the future and its control in Massachusetts can be achieved by two methods. The first is the prevention of the infection of Massachusetts mosquitoes by gametocyte carriers who may act as the source of the epidemic, through adequate treatment and screening of patients. This method, however, is not entirely dependable, since it is impossible to ascertain which asymptomatic persons are gametocyte carriers, and tests that could determine the presence of gametocytes in the blood of all persons who enter the Commonwealth are both difficult to perform and enforce.
- The second and most practical method of controlling malaria is by an attack on the mosquito vectors. Such an attack, however, must be based on accurate knowledge of the distribution of the vectors. The recording of data on the seasonal prevalence and geographic distribution of the mosquito vectors of malaria is one of the accomplishments of the mosquito survey,⁴⁷ conducted by the Massachusetts Department of Public Health in 1939. The United States Public Health Service,³⁷ assisted by state and military agencies, is making detailed surveys of extracantonment areas of military establishments where malaria patients are likely to be hospitalized.
- Should there be any evidence of spread, mosquito-control measures must be directed against those mosquitoes that are carriers of disease, the number of vectors thus being lowered to a number that is insufficient either to maintain the existence of malaria or to permit its introduction.
- It is unlikely that malaria will again become endemic in Massachusetts as a result of this war. Sporadic cases may occur, but any larger outbreak will probably be short-lived and geographically limited. Under proper safeguards, Massachusetts and most of New England are relatively safe from any extensive epidemic of malaria.
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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30121

PRESENTATION OF CASE

A forty-seven-year-old housewife entered the hospital because of pain in the lower back.

The patient had been in apparent good health until one year prior to entry, when, following a cold, she developed a burning pain over the sacrum and lower back. Similar attacks recurred and apparently progressed in severity. Recently the attacks had lasted for three or four days and had forced her to remain in bed. She felt that she was never free of pain, although it rarely kept her awake. During acute attacks, hot packs and aspirin gave relief. About eight months before admission she noticed that the pain radiated to both legs. This was brought on chiefly by sitting for some time and then trying to stand up. She was unable to lift her legs, and attempts to move the thighs brought sharp shooting muscle pains, radiating from hip to knee. At the same time she noted a dull aching pain in the thigh muscles at intervals of about a month, which lasted three to five days. About one month before admission she developed a feeling of fullness and pressing down in the rectum, which was especially noticeable after sitting for some time. Bowel movements did not relieve the sensation. She had had a three-day episode of watery diarrhea with a small amount of blood. She had had night sweats for one year, which were said to be due to the onset of the menopause.

Nine years before entry it was discovered that the patient's serum gave a positive serologic test for syphilis; the spinal fluid was negative. She received antisyphilitic treatment for several weeks at that time, and a full course of treatment seven years later. One year before admission she had a left radical mastectomy for scirrhous carcinoma with axillary metastases, which was followed by x-ray treatment.

Physical examination showed a well-developed, fairly well-nourished woman in no distress. The incision over the left breast was well healed, and no evidence of recurrence could be found. The lungs were negative except for a few moist rales at the left base. The heart was normal. The abdomen

was protuberant. There was increased lumbar lordosis. The posterior superior iliac spines were above the anterior superior iliac spines. Examination on standing showed full spinal motion; on flexion and extension from a flexed position, considerable pain was present about the sacrum. There was joint tenderness over the coccyx, over the sacroiliac joints posteriorly and along the attachments of the erector spinae muscles to the sacrum. In the sitting position passive movement of the spine was normal. Straight leg raising was 60° bilaterally, with stretching of the hamstrings. Rectal examination showed tenderness over the coccyx. Neurologic examination was negative.

The blood pressure was 140 systolic, 100 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a white-cell count of 7700. The hemoglobin was 75 per cent. The urine was negative. Blood Hinton and Wassermann tests were negative. The blood sedimentation rate was 5 mm. in fifteen minutes, 38 mm. in thirty minutes, 49 mm. in forty-five minutes and 51 mm. in sixty minutes. A blood calcium was 11.1 mg. per 100 cc., the phosphate 4.7 mg., and the alkaline phosphatase 8.8 Bodansky units. Two lumbar punctures gave clear fluid with total protein of 53 mg. per 100 cc., a gold-sol curve of 0010000000 and a negative Wassermann reaction.

X-ray examination of the chest showed some scarring in the right upper lung field but was otherwise negative. The heart and mediastinum were slightly displaced to the right. Plain and special films of the lower spine revealed an area of rarefaction in the upper margin of the right sacroiliac joint that was surrounded by dense bone (Fig. 1). There was no evidence of disease in the lumbar vertebrae or pelvis. A barium enema was negative.

The aches and pains in the thighs continued. There was considerable weakness. On the fourteenth hospital day the patient developed a slight sore throat and a feeling of exhaustion. The temperature was 102°F. Rales were heard in the left base, with increased bronchophony. The white-cell count was 21,300. Throat culture yielded a beta-hemolytic streptococcus. She was given intravenous fluids and recovered completely from this infection.

On the thirty-fifth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. THOMAS J. ANGLE: May I see the x-ray films

DR. LAURENCE L. ROBBINS: This is the rather sharply circumscribed area of rarefaction with dense margins that was described. Other than that I do not believe there is anything definite. These areas of calcification are within the abdomen. About the only thing that is at all suspicious is some questionable decalcification in the sacral region.

*On leave of absence.

DR ANGLEM: Can you tell me more about the nature of the radiating pain that extended down the thighs? Was it sciatic in distribution?

DR JOHN REIDY: At times she did have a radiating sciatic pain. In the examinations before admission to the hospital the pain had been of that description, but it subsided, particularly after rest in the hospital.

DR ANGLEM: We have as the essential features of this case a history of pain in the lower back and

slight sore throat. From this she appears to have made a good recovery.

The whole picture is complicated by the fact that the patient is known to have had syphilis in the past, carcinoma of the breast one year before, and x-ray evidence of old pulmonary tuberculosis.

The findings of possible significance are pain referred to the sacral and lower lumbar areas on motion and tenderness on palpation of the sacrum, the coccyx and the regions of the insertion of the



FIGURE 1 Roentgenogram Showing the Area of Rarefaction in the Right Ilium

sacrum of one year's duration, with the development four months later of a radicular type of pain radiating into the lower extremities. The pain appears to have been continuous, with recurring superimposed acute exacerbations of acute pain. Severe shooting pains were induced by lifting the legs. One month before admission the patient developed a feeling of pressure referred to the rectum that was not relieved by evacuation. She had one episode of diarrhea with blood in the stools, which lasted for three days. She had had night sweats for one year, which were ascribed to the menopause but may have arisen on some other basis.

After admission the patient developed a respiratory infection associated with weakness and exhaustion. This is described as a slight sore throat, but the constitutional symptoms seemed to have been severer than those one would expect from a

erector spinae muscles. Also of considerable significance in a negative way is the absence of neurologic signs. The increased sedimentation time and the slight increase in alkaline phosphatase may be of significance, but they are not diagnostic. The increased spinal-fluid protein I believe to be of considerable significance. The x-ray findings may be independent of or related to the patient's present illness.

The symptom complex that this patient presents—pain in the lower back associated with radiation of pain of the radicular type into the lower extremities—is characteristic of a space-occupying lesion in the spinal canal involving the lower spinal nerve roots. Such a space-occupying lesion may arise from a variety of causes. Syphilis should be mentioned because of the patient's past history. It is, however, an uncommon cause of this type of

pain, and since the recent blood and spinal-fluid Wassermann reactions were negative, I believe we can disregard it.

Is there a chest film? The description of the film in the history suggests healed tuberculosis.

DR. ROBBINS: There is evidence of old tuberculosis.

DR. ANGLEM: But no sign of activity?

DR. ROBBINS: Nothing I can be sure of.

DR. ANGLEM: Tuberculosis may produce symptoms of this type when there is tuberculous involvement of the lower lumbar vertebral bodies with extension of tuberculous granulation tissue into the region of the spinal roots. There is, however, no evidence of such involvement in the lumbar vertebrae to support this diagnosis.

The symptoms that this patient presented frequently arise on the basis of a protruded intervertebral disk. The story is characteristic except in certain minor respects — the absence of paresis and of any disturbance of the reflexes, which, however, are not essential for that diagnosis.

The onset is said to have followed a "cold." This cold may have been a nasopharyngitis, which is a not uncommon primary focus from which osteomyelitis develops. A low-grade osteomyelitis of the lumbar vertebrae could produce the symptoms of which this patient complained, through formation of an abscess extending into the epidural space. The x-ray films, however, show no evidence of such a disturbance of the lumbar vertebrae.

I find it difficult to relate the area shown by x-ray in the region of the right sacroiliac joint to this patient's symptoms. It does not have the usual features of metastatic cancer, and in view of its unilateral position and its circumscribed character, I do not believe that it is possible to account for the patient's bilateral symptoms on this basis. I believe we can safely disregard it.

A primary or metastatic tumor involving the cauda equina must be considered. Against a primary tumor are the relatively slow progress of the disease and the complete absence of definite neurologic signs after the duration of a full year. The same argument may be offered against a diagnosis of metastatic tumor. If she had had metastatic disease involving the cauda equina, originating from the breast carcinoma, I should expect it to have progressed more than it had in the course of a year and to have shown evidence of bone destruction by that time. Considering these various possibilities it seems to me that the basis of this patient's complaint was independent of the other diseases of which we have previous knowledge; hence, I believe that she probably had a protruded intervertebral disk.

DR. BENJAMIN CASTLEMAN: Would you like to express an opinion, Dr. Smith-Petersen?

DR. MARIUS N. SMITH-PETERSEN: I know the diagnosis. I, too, belittled the presence of the area

in the posterior iliac crest. I thought that the changes seen in the x-ray film were due to surface changes, which often give an area of increased density surrounding an area of decreased density, but I was willing that the biopsy should be performed.

DR. PAUL ZAMECNIK: When axillary metastases are found, what are the statistics on finding further metastases? I have an impression that they are rather high.

DR. CASTLEMAN: The prognosis is poor in 75 per cent of the cases.

DR. ANGLEM: I considered another possibility, osteoid osteoma, based on the description and the appearance of the lesion in the sacroiliac area, but I did not see how the other symptoms could be explained on that basis.

DR. CARROLL B. LARSON: We explored the sacroiliac region for the lesion that was seen by x-ray and we came down on an absolutely circumscribed area, as shown in the x-ray. A cross section of this area revealed a cellular-appearing homogeneous pinkish-gray material. I could make nothing out of it grossly. We excised the lesion entirely, and in so doing we uncovered a portion of the sacral side of the sacroiliac joint, including the cartilage. The trabeculation in the anterior body of the sacrum appeared abnormal. I cannot tell why, but it just did not look right, so I scooped out some of the material, which was very friable, and sent it as separate and distinct specimen from the lesion in the ilium.

CLINICAL DIAGNOSIS

Osteochondroma of ilium.

DR. ANGLEM'S DIAGNOSIS

Protruded intervertebral disk.

ANATOMICAL DIAGNOSES

Metastatic carcinoma of sacroiliac region.
Fibrous dysplasia of ilium.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The microscopic examination of the material scooped out of the sacrum showed metastatic carcinoma. The well-circumscribed lesion in the ilium proved to be an area of fibrous dysplasia completely surrounded by metastatic cancer, but there was no carcinoma within the cyst-like area. The cancer, therefore, was not seen on the x-ray film.

CASE 30122

PRESENTATION OF CASE

A sixty-nine-year-old woman was admitted to the hospital for study.

The patient was rather confused and unable to give an accurate history. She had had rheuma-

ever as a child. Thirteen years before entry she had an episode of jaundice relieved by the removal of the gall bladder, which was said to have contained stones. Five years prior to entry, she had pain in the right flank radiating to the groin, nocturia, urgency, frequency, dysuria and pyuria. These continued off and on, and she was told that she had gravel in the urine. Two or three years before admission she was found to have an enlarged spleen and anemia; she subsequently had frequent attacks of anorexia, nausea without vomiting, gas and abdominal discomfort. One and a half years before admission, following an automobile accident, she developed intermittent attacks of dizziness, vertigo, tinnitus, headache, diplopia, soreness of the neck and tremors. One year before entry she had epistaxis on several occasions, but had had none since. During the eight months preceding admission she had had frequent loose, dark, watery stools, which had recently become normal following her use of Peptobismol. She had had ankle edema and dyspnea on exertion for several years, but these had increased in severity during the last few months before entry, and she developed occasional recordal pain on exertion. During this period she had considerable pain and stiffness in the back, right leg and both arms, and occasionally in the chest. She had lost about 40 pounds of weight over a period of years.

She had had several admissions to the Massachusetts Eye and Ear Infirmary for sinus trouble, bilateral cataracts and other eye troubles.

Physical examination showed a well-developed, rather obese woman in no distress. There was no enlargement of the lymph nodes. She was edematous. The tongue was smooth. The left half of the diaphragm was elevated. The lungs were clear. The left border of cardiac dullness was 12.5 cm. from the midline in the fifth space. The sounds were regular except for occasional extrasystoles. A loud harsh systolic murmur was heard at both the apex and the base, but chiefly in the aortic area. A mitral diastolic murmur was also heard by one observer. The aortic second sound was greater than the pulmonic. The abdomen was protuberant and diffusely tender. A large mass was present in the region of the spleen, extending anteriorly to the midline and five fingerbreadths below the costal margin. The mass was smooth, movable, ballotable and tender, and moved with respirations. There was some tenderness in the left costovertebral angle. Pitting edema of the ankles and sacrum was present. Neurologic examination was normal except for diminished vibration sense in the left leg and absent ankle jerks.

The blood pressure was 146 systolic, 90 diastolic. The temperature was 98.6°F., the pulse 80, and the respirations 20.

Examination of the blood showed a red-cell count of 3,680,000, with 64 per cent hemoglobin. The

white-cell count was 2200, with 64 per cent neutrophils, 32 per cent lymphocytes and 4 per cent monocytes. The platelets were diminished in number, and the red cells were hypochromic. The urine was cloudy, with a pH of 7.5 and a specific gravity of 1.012. There was a + test for albumin, and 1 or 2 red cells per high-power field in the sediment. The stools were guaiac negative. The nonprotein nitrogen was 10 mg. per 100 cc., the blood calcium 10.1 mg., and the phosphorus 1.6 mg. The phosphatase was 4.1 Bodansky units. A blood Hinton test was negative. The blood protein was 6.6 gm. per 100 cc., the albumin being 3.4 gm. and the globulin 3.2 gm. The van den Bergh test was normal.

X-ray examination showed the heart to be enlarged to the left. There was some fullness in the region of the left auricle. The lung roots and fields were not unusual. A large mass was seen in the left abdomen; this was separated from the kidney but not distinguishable from the spleen. The left kidney was somewhat larger than usual. There was an opacity in the right upper quadrant the nature of which could not be determined. There were hypertrophic changes in the spine.

X-ray films of the skull were not remarkable. A barium enema revealed normal filling of the colon. The splenic flexure was displaced anteriorly by an enlarged spleen. A gastrointestinal series was negative except for several longitudinal varices in the lower esophagus. An intravenous pyelogram was somewhat unsatisfactory because of the previous barium. No definite stones could be seen, and except for a slightly low position of the left kidney, no evidence of disease of the urinary tract was observed.

After the first day or two, the patient complained of pain and burning on urination. The urine was found to contain innumerable white cells. A culture gave many colonies of colon bacilli. On the eighth day she was given 4.5 gm. of sulfadiazine, followed by 2 gm. daily for the next three days, at the end of which time the urine had cleared up considerably. The white-cell count was 1800, with 65 per cent polymorphonuclears, 27 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. The platelets were still decreased in number. The hemoglobin was 7.5 gm. per 100 cc. On the fifteenth day a cephalin flocculation test was ++++ in twenty-four hours and ++++ in forty-eight hours. The prothrombin time was 28 seconds (normal, 18 seconds). The hematocrit was 34 per cent. There was 60 per cent retention of bromsulfalein at the end of forty-five minutes.

The patient was given intramuscular injections of liver extract, 15 units daily. On the eighteenth day she had a severe shaking chill with a fever of 101°F. In the next two days she had colicky pain in the right costovertebral angle and flank. She was nauseated but did not vomit. Examination

showed extreme tenderness in the right-costovertebral angle and flank. One urine examination gave a ++ test for albumin, with a specific gravity of 1.010 and innumerable red cells. An examination on the following day showed large numbers of white cells.

On the twenty-first day the patient had a chill with elevation of temperature to 106.4°F. A blood culture yielded colon bacilli in both flasks. The white-cell count was 1500, and the red-cell count 3,190,000 with 7.5 gm. of hemoglobin. She was given a transfusion of 500 cc. of blood, followed by sulfadiazine for the next two days. The temperature remained elevated, and the pulse became irregular, rapid and of poor quality. There were basal rales. She was given 4 cc. of Cedilanid intravenously, and intravenous saline in glucose and sodium sulfadiazine, but died on the twenty-third hospital day.

DIFFERENTIAL DIAGNOSIS

DR. CHESTER M. JONES: One of the things that impresses me is that more and more at these conferences we are getting patients farther along in life, thus increasing the necessity for a multiplicity of diagnoses. Many different things happened to this woman that ought to be remembered in the subsequent events. She had had rheumatic fever, jaundice, gallstones, renal colic, an enlarged spleen and anemia. There is also a good description of the symptoms of a subdural hematoma. One year before entry she had epistaxis on several occasions, which is just one more item that adds to the confusion of the story. She had had loose stools, which possibly were tarry, and finally, symptoms of pericardial pain, exertional dyspnea and pain in the extremities and chest. The cataracts and other eye troubles are further evidence of degenerative disease.

It seems to me that with this clinical story it is simply a question of adding up the facts and presenting them as probabilities. I do not see any reason for assuming that there was some rare condition. She had had rheumatic fever and presented the physical signs that are consistent with old, healed mitral stenosis. She is said to have had a mid-diastolic murmur, which is characteristic of this condition.

DR. PAUL D. WHITE: What about the aortic valve?

DR. JONES: She could have an old rheumatic involvement of the aortic valve as well. There is no story of a thrill, transmission of that murmur or a wide pulse pressure.

According to her testimony she had gallstones, which gallstones were removed, and she had jaundice in one of the attacks preceding operation. At entry, the x-ray studies are said to have shown a homogeneous mass in the right upper quadrant whose nature could not be determined. I cannot

do any better than to guess that that might conceivably have been a gallstone that was still in the common duct. The most that I can say is that she had had gall bladder disease in the past — gallstones and jaundice — and had the makings of chronic intrahepatic disease because of the persisting attacks.

There is a perfectly good story of renal stones, and there is no reason to think that the patient did not have them. She had pain in the right flank radiating to the groin, nocturia, frequency, urgency and pyuria. There was evidence of urinary-tract disease during her stay in the hospital, in that she had pain and tenderness in the right costovertebral angle, right pleural pain, a shaking chill, and urine that contained on one occasion red cells and on another pus. There were colon bacilli in the urine, and it is not unreasonable to think she had a urinary-tract infection arising from gravel or stone in the right kidney, which could logically explain the signs and symptoms she showed in the hospital. Whether the hematuria was due to an intrarenal tumor is a matter of pure speculation.

She was said to have had an enlarged spleen and anemia three years before she came in, and I see no reason to doubt that — in other words, she may have had so-called "Banti's disease" as a result of thrombosis of the splenic vein. There is, however, no episode to suggest such a diagnosis. The finding of Banti's disease in a person of her age is unusual. Therefore, it seems to me wiser to admit that she had something more than involvement of the splenic vein, in which case one wonders about intrahepatic disease — cirrhosis of the liver with splenic enlargement. We know that she had esophageal varices by x-ray and also leukopenia, findings that go with any chronic serious intrahepatic lesion even when the disease is relatively quiescent. A splenic tumor fits in with chronic liver disease, and varices can be associated with portal hypertension rather than with thrombosis of the splenic vein. On the basis of the laboratory findings we know that there was a serious intrahepatic complication: the cephalin flocculation test was ++++, there was marked dye retention and the prothrombin time was increased.

The attack of dizziness and vertigo, a year and a half before admission, following the automobile accident, makes me wonder if she had concussion and a subdural hematoma. At any rate these symptoms date from the accident. The nosebleeds may have been due to focal venous engorgement or she may have had marked hypertension, which she did not have on arrival at the hospital. One would have to guess rather than state that she had hypertension. The dark watery stools I cannot explain, unless one wants to say that she was bleeding from esophageal varices.

The patient had precordial pain on exertion, ankle edema, dyspnea and shortness of breath, and it seems

reasonable to suppose that they were cardiac in origin. She was sixty-nine years old when she developed the symptoms, and they appear to have been associated with a degenerative process—namely, arteriosclerotic disease involving the coronary vessels as well as other vessels in the body. She probably had arteriosclerotic disease in addition to the old mitral lesion.

The pain and stiffness in the back, right leg and both arms and the pain in the chest are general complications that occur in any older patient who is "aching all over." She undoubtedly had degenerative changes in the bones, and I assume that she had hypertrophic arthritis. That could explain the aches and pains that she noted from time to time. The loss of 40 pounds of weight over a period of years, and not just during the year prior to admission, I tie in with generalized arteriosclerosis, chronic intrahepatic splenic disease and possibly inadequate diet, along with some degree of heart failure. She had a smooth tongue, diminished vibration sense and absent ankle jerks. If these findings are correct, they are consistent with vitamin deficiency.

The elevation of the diaphragm on the left can be explained by the enlarged spleen. The heart was enlarged to the left. As I have already mentioned, there was a systolic murmur at the base and a diastolic murmur characteristic of mitral disease at the apex. I suppose that might be an Austin-Flint murmur, but I am inclined to doubt it.

The white-cell counts were consistently low. That is consistent with the chronic intrahepatic disease and splenic enlargement, sometimes called "Banti's disease," although I think that the term should be reserved for those cases that have primary disease in the spleen rather than in the liver. The red cells were hypochromic, a fact consistent with bleeding from the gastrointestinal tract. The nonprotein nitrogen was low, and there was fixation of the specific gravity of the urine—1.010 to 1.012. Undoubtedly there was renal involvement of a degenerative nature, possibly with infection. On the other hand, a low nonprotein nitrogen is consistent with serious liver disease. The albumin-globulin ratio was approximately 1.0, also suggesting liver disease. The spleen was enlarged both by physical examination and by x-ray. I should like to look at the films. Did any of them show a gallstone or a large mass in the right upper quadrant?

DR. MILFORD SCHULZ: This shadow probably represents a calculus in the lower pole of the kidney.

DR. JONES: Then I withdraw the remark about gallstones. This picture is quite different and should have been mentioned in the original description of the x-ray findings.

DR. JOSEPH AUB: Is the left kidney enlarged?

DR. SCHULZ: Both kidneys are good sized, and I do not see any real deformity of the calyces. All the bones of the pelvis and spine seem to be intact.

The evidence of mitral disease apparently was more prominent when observed fluoroscopically than is shown on the film.

The films of the gastrointestinal tract show an essentially normal stomach, but in the esophagus there are definite varices. I assume that the films of the skull were taken because of the previous head injury or possibly for examination of the bones.

DR. JONES: From these films it seems to me that there is no reason to change any of the possibilities except to add one as a probability rather than a possibility. I agree with Dr. Aub that the left kidney looks enlarged.

What happened in the hospital is of interest. The patient had an episode of right-sided renal pain with costovertebral tenderness, and I assume that she probably had a calculus, with resulting blood in the urine, fever and chills. Because of that fact it seems reasonable that the shadow in the region of the right kidney is consistent with stone. Is that not correct, Dr. Schulz?

DR. SCHULZ: Yes; it seems to be in the lower calyx.

DR. JONES: The patient had a story of previous renal colic, probably with infection. We know that she eventually developed terminal sepsis and that colon bacilli were found in the urine.

What are the conditions to be found in this woman? I think that she had old rheumatic heart disease with mitral involvement, and probably generalized arteriosclerosis with involvement of the heart. It is quite possible that arteriosclerotic heart disease rather than rheumatic heart disease was of more importance in relation to the heart failure and precordial pain on exertion. She had degenerative changes in the spine. She probably had cirrhosis of the liver with a relatively small liver and an enlarged spleen and resulting portal hypertension and esophageal varices. She did not have a primary hepatoma on top of the cirrhosis. I do not see how one can avoid the evidence of real interference with hepatic function and I do not believe it was entirely on the basis of cardiac failure. She undoubtedly had some changes in the right kidney, probably pyelonephritis as well as arteriosclerotic changes. I do not know the cause of the apparent renal enlargement on the left. There was no hydronephrosis. The ureter was not noted to be enlarged, and on the x-ray films its shadow appears to be normal. Is that correct, Dr. Colby?

DR. FLETCHER H. COLBY: From here the renal outline appears to be fairly large but not irregular. There is no depression of the calyces that I can see. I do not believe that there was a renal tumor.

DR. JONES: To say that she had a tumor is simply a guess to explain an unusual finding in the kidney. I think that she had right renal colic from a renal calculus, with resulting infection. I do not believe that she had gallstones.

DR. AUB: Could she not have some widespread degenerative disease, such as amyloidosis?

respiratory infections, and there was no significant difference in the average duration of illness in the two groups. The total number of organisms recovered in periodic throat cultures made in the sulfadiazine-treated children was not less than that in the controls. Some types of organisms were entirely unaffected by the drugs, whereas others were strikingly reduced in number, particularly the gram-negative cocci (*Neisseria*). After one month of treatment, however, these organisms again increased, and sulfadiazine-resistant strains were encountered. Similar changes were noted among pneumococci. In the control children many types of pneumococci were encountered continuously throughout the study. In the treated group, on the other hand, the same multiplicity of types was noted at first but within a short time only two types dominated. Tests showed that these two types had become sulfadiazine resistant, and shortly thereafter these same sulfadiazine-resistant strains of pneumococci had spread into the throats of the control group of children, who were housed in the same cottage.

The results of these investigations suggest another possible danger, and a serious one, from the prolonged use of sulfonamide drugs in prophylaxis or treatment. The question is raised whether these drug-resistant virulent strains will eventually lead to infections that are difficult to manage and to control. The development of such strains during the treatment of disease has already been encountered.³ Julianelle and Siegel correctly point out that further studies are needed to determine whether these drug-resistant strains really constitute a practical hazard in the prolonged use of the sulfonamides.

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SURVIVAL OF THE FIT

CHANGES in the environment, sometimes slow, sometimes rapid, and the adaptation of life to them, are being constantly demonstrated, and natural history, so far back as discoverable records go, shows

that those forms of life that could not adapt themselves to changes in their surroundings had perished. The sabre-tooth tiger and the mastodon, once lords of the terrain over which they roamed, are known to us only through crude, prehistoric drawings and an occasional pile of mud-encrusted bones; the giant saurians, maintaining themselves on the lush vegetation of the muck age, succumbed when these conditions changed, and have left us to remember them by, only their skeletons and a gigantic footstep.

It is important to note, however, that no biological order has completely disappeared from life. We have tigers and elephants and lizards, but of different and varieties and characteristics suited to their continued existence in the medium in which nature left them, so long as that medium remains suitable to them. The working theory of the survival of the fittest has seen to it that the correct animal was left to graze in its proper pasture; that a suitable vegetation succeeded in the soil and climate best adapted to it; that those organisms hardy enough to withstand the inimical forces of nature are the ultimate survivors until, perhaps, some new influence requires a greater refinement in the strain or allows a newly originated species to flourish.

Thus in the vegetable kingdom we find resistant strains of wheat and other food crops; flowers; blight-resistant chestnuts are appearing after the apparent destruction of our chestnut some years ago. The human race is developing resistance, perhaps owing both to mass immunization and to natural selection, to many of the infectious diseases that have variously scourged it. Syphilis, although still an ubiquitous plague, is not so sear as it did when it was first visited on our kind; tuberculosis finds fewer victims and ravages them less fiercely than when consumption took toll of the last few centuries — an improvement is not entirely due to better hygiene and to finding; and measles is a relatively minor annoyance among conditioned populations, as compared with the havoc it can raise on virgin soil, such as existed on Pitcairn and among the Faroe Islanders.

Even as we develop our immunities and our weapons for defense, however, our biologic enemies adapt themselves to the new conditions with w

challenge them, and the battle is never entirely
1. Even new and better chemical agents will not
ish the last word against infectious disease,
uable as they have proved themselves to be, for
human body may become sensitized to them, and
g-resistant strains of various pathogenic organ-
s put in their appearance. Cases of pneumo-
cal pneumonia are encountered, for example, that
not respond to sulfonamide therapy, and the in-
ence of gonococcal infections that are resistant to
motherapy is appreciable. The same, no doubt,
be true with penicillin and every other agent
t we may develop. The struggle is unremitting.

DICAL EPONYM

RIER'S DISEASE (PSEUDOXANTHOMA ELASTICUM)
ean Darier (b. 1856), of Paris, presented a paper
seudoxanthoma elasticum" at the Third Inter-
national Dermatological Congress in London during
gust, 1896. A German translation of this paper,
Dr. Turkheim, of Hamburg, appeared in the
natshefte für praktische Dermatologie (23:609-
, 1896). A portion of the translation follows:

There is a disease of the skin, apparently of rare occur-
rence, with clear, unmistakable anatomic and clinical
ptoms that can be termed "pseudoxanthoma elasticum."
This disease expresses itself clinically by the formation
of macules, plaques or yellowish papules that have great
milarity to those of true xanthomas.

Anatomically, the disease finds its expression in a dis-
ruption with swelling and finally disintegration of the
lastic tissue into absolute crumbs . . . On the other
and the specific metamorphoses of xanthoma, xan-
thomatous cells and fat granules are missing.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE TO AID THE STRICT RATIONING OFFICER

Requests for extra rations on medical certificates
patients' necessity, above and beyond the basis
els to which the population as a whole has cheer-
ly submitted, continue to come in to the local
rationing boards at a fairly steady rate. Those that
eed certain established maximums or concerning
ich any particular question is raised are usually
ferred to the regional Office of Price Administra-
1 to be passed on by the advisory medical
nmittee.

Some rationing boards, such as the Brookline
ard, have appointed local medical advisory com-
tees; such a course, if widely followed, would
ve to lighten considerably the load of the regional
ce, especially if existing formulas were accepted
a spirit of co-operation. It must be re-emphasized
at the advisory committee of the Massachusetts
ical Society is desirous only of helping to apply

the principles of food rationing in such a way that
as little hardship as possible will be inflicted on any-
one. Furthermore, it believes that basic rationing as it
applies to the majority of persons carries no hardship.

It has been possible at last to obtain reasonably
accurate figures on the number of persons obtaining
extra ration allowances from one large community—
Somerville. In that city, 0.5 per cent of the popula-
tion is receiving supplementary food allowances—
on the whole, not a staggering proportion of the
residents.

The alluring diagnosis of anemia is assuming in-
creasing prominence as a reason for the prescription
of extra rations, especially red meats and liver. In
reference to this situation, it must be pointed out
that anemia is not included in the legitimate
extra-point diseases listed by the Subcommittee on
Medical Food Requirements of the National
Research Council; that hematologists have ven-
tured the opinion that iron and liver extract are
more effective antianemic substances than is meat;
and that in England liver is considered too precious to
use as food, being reserved for the preparation of liver
extract for the treatment of hyperchromic anemia.

JOSEPH GARLAND, *Chairman*

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

WEISSMAN—Robert J. Weissman, M.D., of Bristol,
died February 1. He was in his thirty-third year.

Dr. Weissman received his degree from the University of
Vermont College of Medicine in 1937. He first interned in
Louisville, Kentucky, before setting up a practice in Rich-
mond and Montpelier, Vermont. Dr. Weissman had been in
Bristol about three years.

His widow and mother survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN

CLINIC	DATE	CLINIC CONSULTANT
Salem	April 3	Paul W. Hugenberger
Haverhill	April 5	William T. Green
Lowell	April 7	Albert H. Brewster
Springfield	April 12	Garry deN. Hough, Jr.
Brockton	April 13	George W. Van Gorder
Pittsfield	April 17	Frank A. Slowick
Worcester	April 21	John W. O'Meara
Fall River	April 24	Eugene A. McCarthy
Hyannis	April 25	Paul L. Norton

MISCELLANY

WARREN TRIENNIAL PRIZE

The Warren Triennial Prize, which was founded by the late
Dr. J. Mason Warren in memory of his father and which
carries an appreciable honorarium for the best dissertation,
considered worthy of a premium, on some subject in physi-
ology, surgery or pathology, was recently awarded by the
General Executive Committee of the Massachusetts General
Hospital to David G. Cogan, M.D., V. Everett Kinsey, Ph.D.,
and Erwin O. Hirsch, B.A., for their essay entitled
"Physiologic Studies on the Cornea." The paper "Studies
on Traumatic Shock," by Everett I. Evans, M.D., received
honorable mention.

CORRESPONDENCE

ATHEROSCLEROSIS

To the Editor: How difficult the task of making plain to the generality of the profession the significance of retained cholesterol esters is going to be is indicated by the reaction of a brilliant man like Dr. Roger I. Lee (Geriatrics: The medical care of the elderly. *New Eng. J. Med.* 230: 190-193, 1944) to the thesis that this agent is the cause of atherosclerosis. Let me say in the beginning that the term "atherosclerosis" is not mine. Recognition of the distinctive character of the disease goes back to Virchow and Aschoff. The contradictory name atherosclerosis (literally, mushy hardening) goes back to Marchand. The term is not limited in its application to "premature and devastating arteriosclerosis." It is applied to the important form of arteriosclerosis that is probably responsible for at least 90 per cent of clinical and pathologic manifestations of arteriosclerosis as such.

The sterols are evidently necessary to life since they are found in all living cells, animal and vegetable. Cholesterol is one of the most complex substances found in the animal body (Schoenheimer). It is so complex that we do not know how it is metabolized. We do know, however, that its metabolism is difficult, and that when the substance is present in excess it is precipitated in crystalline ester form in the tissues and is treated as a foreign body. It is engulfed by phagocytic cells and is carried in these cells into the arterial intima. The characteristic that differentiates atherosclerosis from other forms of arterial disease is the presence in its lesions of crystals of excess cholesterol, usually in ester form, and visible under polarized light. We do know that excess ester cholesterol is a chronic irritant comparable to silica sol. We do know that excess cholesterol satisfies all of Koch's postulates as the cause of atherosclerosis.

Dr. Lee makes much (or little) of the use of the rabbit for experimental purposes. The old criticism that the rabbit suffers an artificial disease because we introduce into its diet an animal fat to which it is not accustomed does not carry much weight when one remembers that much of the knowledge we have of human infection and immunity arose from the introduction into rabbits of bacteria or toxic agents to which they were not accustomed. It is also to be remembered that the rabbit synthesizes this same animal fat (cholesterol) for the needs of its own cells. Moreover atherosclerosis has been produced in chickens by adding excess cholesterol to their diet (Dauber, D. V., and Katz, L. N. Experimental cholesterol atherosclerosis in an omnivorous animal. *Arch. Path.* 34:937-950, 1942). As a matter of fact the principal function of rabbit experimentation has been to satisfy Koch's postulates and to clear up the *modus operandi* of excess cholesterol activities. Our basic knowledge of the causation of the disease is due to the study of the specific relation of excess cholesterol esters to the lesions of human atherosclerosis, and is particularly due to the following of the disease sequence (Sydenham's footsteps of disease) from beginning to advanced stages in some thousands of human lesions.

Cholesterol is the forerunner of the cortical adrenal secretion. It is the probable source of the bile acids and the sex hormones. Its degradation products include known carcinogens. A retained excess of cholesterol is potentially dangerous. There is evidence of its pathogenic action in the human body in addition to the causation of atherosclerosis. Excess cholesterol is manifestly a substance that should be destroyed or excreted. We are able to metabolize it in youth, as is shown by its removal from the ester deposits in the aorta in the atheromas of infancy and puberty. It is this ability that prevents the production of atherosclerosis in the arteries of youth.

As we age we lose the power to control cholesterol. There is no longer a metabolism that can destroy the excess, and no excretory machinery that can remove it from the body. It remains within the body and is responsible for the production of the condition that led Dr. Lee to conclude: "No, that isn't wear and tear; that is just rust." Modern industrial chemistry is demonstrating new methods to prevent rust. It is my expectation that modern medical methods, no longer influenced by the "abandon hope" attitude adopted in so-called "modern" texts on geriatrics, will find means of preventing or controlling the "rust" that can kill men even in the twenties and thirties from coronary disease, and

can lift cardiovascular renal disease and cancer to a of domination of the causes of death as early as the f

TIMOTHY LEAR

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CANDIDATES FOR INTERNSHIPS

To the Editor: At a recent meeting of the War Post Committee of the Massachusetts Medical Society Edward A. Knowlton, of Holyoke, raised an in question. He asked how hospitals approved for training should attempt to procure interns.

Under the accelerated program and the 9-9-9 plan all medical students who are in their final year, e to graduate in the fall of 1944, have been appointed t ships that will begin about October 1 and will en July 1, 1945. A number of hospitals already are begi scrutinize, as potential intern candidates to succee third-year medical students, who so far have had than a few months' exposure to clinical work of any

The Boston Interhospital Internship Commit decided to hold on October 16 to 19, 1944, its examin the next group of internships available under its juri This committee considers it unsound to examine d idates until they have completed at least three full medical education. Not before then can they be to have had enough clinical work to be in a position the type of internship that they wish to undertake; before then can their teachers have a valid opinion co their ability as clinicians.

The internship is such an important part of medic tion and interns are such an essential part of hospi ciency that their proper selection under war condit most important step. Their premature appoint unnecessary and does not seem sensible.

REGINA

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"HOLMES AS A PSYCHIATRIST"

To the Editor: My attention has been called to statements in the editorial *Holmes as a Psychiatrist* published in the February 3 issue of the *Journal*.

The first relates to the date of the address given by before the Phi Beta Kappa Society at Harvard. used, 1871, was based on a statement by Oberndorf essay *The Psychiatric Novels of Oliver Wendell*. Actually the lecture was given on June 29, 1870, a stated on the title page of the printed address, w not published until 1871. Editions were issued Boston and London in that year, and the address printed, with a new title page, in Boston in 1872.

The editorial stated, moreover, that the address, " held from publication for more than twenty years, after careful revision, expansion and annotation h place, did Holmes allow it to appear in print." above, this statement is entirely incorrect. The add printed not only once but a number of times, and at Holmes made no effort to suppress it himself. W debted to Mr. F. Franklin Currier, the bibliogr Holmes, moreover, for calling attention to a state Holmes in a letter to a classmate: "The sale and of my little book have been quite a surprise to a hardly expected it to pay for itself but so far it remarkably well."

The writer of the editorial misinterpreted a state Oberndorf, who wrote that the essay "was carefully expanded, and annotated before it was printed from an *Old Volume of Life*." This reference sho been verified and not taken to mean that the add not published immediately after it was given. O moreover, is not correct in saying that the add "revised, expanded, and annotated" before it was Even in the 1883 edition of *Papers from an Old Volum* the article contains few revisions.

I am indebted to Dr. George R. Minot for cal attention to these errors.

HENRY R. VIE

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(Notices on page x)

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A CLINICAL EVALUATION OF SULFAMERAZINE*

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BOSTON

THE purpose of this report is to present the results of the treatment of 278 patients with sulfamerazine. This sulfonamide derivative is 2-sulfanilamido-4-methyl pyrimidine (sulfamethyldiazine). Its chemistry has been described by Roblin, Williams, Winnek and English¹ and by Sprague, Kissinger and Lincoln.² In spite of the fact that preliminary studies of experimental infections in animals indicated that sulfamerazine is fully as active as sulfadiazine, it did not until recently receive the attention it deserved.

From the studies of Welch, Mattis, Latven, Benson and Shiels³ and others,⁴ it became apparent that sulfamerazine might have certain advantages over sulfadiazine, provided it could be shown to be as effective in the treatment of infection. These advantages were the greater solubility of both sulfamerazine and its acetyl derivative than the respective sulfadiazines, the more rapid and more complete absorption of sulfamerazine from the gastrointestinal tract and its slower excretion by the kidneys.

When equal doses of sulfamerazine and sulfadiazine were given by mouth to normal subjects, Welch et al. were able to obtain and maintain blood levels of sulfamerazine that were on the average more than double the values obtained with sulfadiazine. These observations naturally suggested that blood levels comparable to those obtained in the clinical use of sulfadiazine could be achieved with a considerably reduced total dosage of sulfamerazine, and that adequate blood levels could be maintained with a longer time interval between doses. Finally, in view of the somewhat increased solubility of sulfamerazine over sulfadiazine, it was suggested that fewer renal complications might occur.

In this study, the purpose was to determine the clinical efficiency of sulfamerazine in various infec-

tions, the adequate dosage schedule and the side reactions.⁵

Before presenting the results it is well to say something about the toxicology of sulfamerazine. Extensive studies of this subject by Welch et al.³ in mice, dogs, monkeys and chickens showed that when similar blood concentrations are maintained, the toxic effects of sulfamerazine are no greater than are those that follow the administration of sulfadiazine. Particular importance was attached to the study of neuropathologic changes in chickens. These experiments showed definitely that sulfamerazine produced fewer lesions of the spinal cord and sciatic nerve of chickens than did sulfadiazine. There was therefore no good reason for believing that sulfamerazine is more toxic to the nervous system than is sulfadiazine.

Preliminary studies of toxicity in man by the same investigators revealed no unusual toxic reactions. This finding has been further supported by similar but more extensive studies by Clark et al.⁶ These authors, after administering sulfamerazine to 200 patients, concluded that sulfamerazine is probably no more toxic than the sulfonamides now in common use.

CLINICAL MATERIAL AND METHODS

In the present study, sulfamerazine was administered to 278 patients with bacterial infections. Two hundred and ten of these patients were adults, and 68 were children under twelve years of age.

As a general rule, adults were given 2 gm. initially, followed by 1 gm. every eight hours thereafter. In children weighing 60 pounds or more, the same dosage was followed. In children weighing less than 60 pounds, the initial dose was usually 0.5 gm. and

*The following articles reporting clinical studies of sulfamerazine have

*From the Evans and Haynes memorials, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

†This work was supported by a grant-in-aid from the Sharp and Dohme Company, Philadelphia.

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§Resident physician, Haynes Memorial, Massachusetts Memorial Hospitals, instructor in medicine, Boston University School of Medicine.

Director, Evans Memorial, Massachusetts Memorial Hospitals, Physician-in-chief, Massachusetts Memorial Hospitals, Wade Professor of Medicine, Boston University School of Medicine.

211-216, 1943.

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the daily maintenance dose was computed on a basis of 0.5 gm. for each 10 pounds of body weight and was given in three equally divided doses at eight-hour intervals. In most of the cases the oral route was exclusively used. In a few severely ill patients, particularly those with meningitis, the sodium salt of sulfamerazine was given intravenously as a 5 per cent solution in distilled water during the early part of their illness. Occasional modifications of the above dosage schedule were necessary. Among the adult cases, the dosage was increased in 17 cases and reduced in 27.

Daily determinations of free and total sulfamerazine were performed on samples of whole blood in most of the cases, and at frequent intervals in the remainder. The method of Bratton and Marshall⁶ was used for these determinations.

Efforts were made to keep the daily urinary output above 1200 cc. In a few cases equal quantities of sodium bicarbonate were given with each dose of sulfamerazine, but this procedure was not followed in the majority of cases.

There was no fixed policy with regard to the duration of therapy. In general, sulfamerazine was continued for a period of forty-eight to ninety-six hours after apparent clinical recovery and the disappearance of fever.

CLINICAL RESULTS

Pneumonia

Eighty-nine patients were treated for pneumonia. In 46 of these the causative organism, as judged by the blood culture or sputum examination, was a pneumococcus, and in 4 it was a beta-hemolytic streptococcus; in the remaining 39 the blood cultures were negative and the organisms cultured from the sputum were not considered to be related to the infection. Of the entire group, 7 patients died, giving a mortality rate of 8 per cent. Of the remaining 82 patients, a clear-cut therapeutic response was observed in 77.

Pneumococcal lobar pneumonia. Forty-four adult patients presenting the typical clinical picture of lobar pneumonia were found to have typable pneumococci in either the sputum or the blood or in both (Table 1). Analyzed from the point of view of factors influencing prognosis, this group of patients was closely similar to the series of sulfonamide-treated pneumonia cases that have been reported by other investigators.⁷⁻¹² Fourteen patients (32 per cent) had involvement of more than one lobe. Twelve patients (27 per cent) had bacteremia. Twenty-four patients (54 per cent) were fifty years of age or older. Five patients (11 per cent) were chronic alcoholics. Seven patients (16 per cent) had organic heart disease with cardiac failure and 5 (11 per cent) suffered from a variety of significant systemic disorders, including diabetes, myxedema, pulmonary tuberculosis and carcinomatosis. For those who recovered without complications, the average dura-

tion of treatment was seven days and the average total dosage was 20 gm. The average blood level maintained through the course of therapy varied from 4 to 17 mg. per 100 cc. of free sulfamerazine and from 5 to 19 mg. of total sulfamerazine.

Four of the patients had received either sulfathiazole or sulfadiazine before entry to the hospital.

TABLE 1. Data on Cases of Pneumococcal Lobar Pneumonia

TYPE OF INFECTING PNEUMOCOCCUS	NO. OF CASES	CASES WITH BACTEREMIA	RECOVERIES	DEATHS
1	7	2	7	
2	1		1	
3	7	1	7	
4	5	3	3	2
5	2		2	
6	1		1	
8	5	2	5	
9	2		2	
10	1	1	1	
12	1	1		1
14	1	1		
15	2		2	
17	2		2	
19	3		3	
25	1		1†	
29	1		1	
32	1		1	
36	1	1	1	
Totals	44	12	40	4
Percentages		27	91	

*All deaths occurred in patients having bacteremia.
†This patient did not respond to sulfamerazine, but subsequently recovered after treatment with penicillin.

These patients were still acutely ill, one of them with a positive blood culture, at the time sulfamerazine therapy was instituted. Three patients received type-specific antiserum in addition to sulfamerazine; 2 died; and 1 developed an empyema.

Thirty-six patients recovered promptly and without complications. Eighteen were afebrile within forty-eight hours; and in 6 more the temperature was normal at the end of seventy-two hours; in the other 12 the temperature fell by lysis over a longer period of time. None of these patients relapsed. Figure 1 shows the chart of a patient who responded promptly to therapy.

Of the remaining 8 patients, 4 eventually recovered. One of these had delayed resolution, experienced a massive sterile pleural effusion, developed an empyema requiring surgical drainage, and the fourth, who was still acutely ill after seven days of therapy, was given penicillin and subsequently recovered.

Four patients died, giving a mortality rate of 11 per cent. The first patient was a seventy-four-year-old man with carcinoma of the prostate and generalized metastases. He was admitted on the fifth day of illness in severe cardiac failure and died four hours later. The blood culture was positive for Type 14 pneumococcus. The second patient was a fifty-year-old man who was admitted with a blood culture positive for Type 4 pneumococcus and a leukocyte count of 1350, no granulocytes being seen on smear. He was given specific antiserum and seemed to be improving until the third day. Atrial fibrillation with pulmonary edema then developed, and he died on the fourth day, apparently

cardiac failure. The third patient was a forty-two-year-old man admitted on the third day of his disease. The blood culture on admission was positive for Type 4 pneumococcus. He was given specific antiserum as well as sulfamerazine, but failed to improve and died in peripheral circulatory collapse on the third hospital day. The fourth patient was a forty-two-year-old man who was admitted on the seventh day of his disease, with a history of chronic alco-

Of these 17 patients, 15 recovered without complications and 2 died. The first death occurred in an eighty-four-year-old man who on entry appeared to be in extremis. X-ray examination showed consolidation of both the left upper and left lower lobes. The patient received 17 gm. of sulfamerazine over a period of six days. Although the signs in the chest had begun to clear, the general condition deteriorated and he died on the sixth day of therapy. The second fatality was in a sixty-eight-year-old man who entered the hospital in congestive heart failure, with a temperature of 104°F. and signs of consolidation of the right lower lobe. He received sulfamerazine for three days, during which time the temperature fell to normal; however, he became progressively more stuporous, lapsed into coma, and died on the third hospital day. No autopsy was obtained in either case.

Streptococcal pneumonia. Four patients with pneumonia caused by a beta-hemolytic streptococcus were treated with sulfamerazine. Three recovered and 1 died. Two of the patients were children in whom the pneumonia was secondary to scarlet fever. The other two were adults in whom the pneumonia was apparently primary. Both children recovered. One of them developed an empyema that had to be drained surgically. This patient received sulfamerazine for twenty-five days, at the end of which time thoracotomy was performed, and the drug was discontinued because of a sharp drop in the white-cell count with depression of the granulocytes. The second child developed a sterile pleural effusion that eventually resolved spontaneously. He received sulfamerazine for twenty-six days, becoming afebrile on the twenty-third day of therapy.

Of the two adult patients, the first was a man fifty-two years of age who had been hospitalized for mild hypertensive heart disease. His course was without event until the end of the third week, when he had a shaking chill, with a rise in temperature to 105°F., and developed signs of pneumonia. Blood culture showed a beta-hemolytic streptococcus. He was given sulfamerazine, with a prompt return of the temperature to normal in twenty-four hours. Although a transient secondary rise of temperature to 102°F. occurred on the fifth day, he had completely recovered after nine days of therapy.

The other adult patient was a sixty-five-year-old man who had been ill for five days before entry. On admission there were signs of pneumonia in the right lower lobe. Culture of the sputum showed an almost pure growth of beta-hemolytic streptococci. Three blood cultures were sterile. On the fourth day of treatment, fluid appeared in the right pleural cavity. Culture of this fluid also showed a beta-hemolytic streptococcus. The patient received 3 gm. of sulfamerazine daily for ten days, during which time the blood levels of the uncombined drug ranged between 5 and 10 mg. per 100 cc. He failed to improve, however, and death occurred on the tenth hospital day.

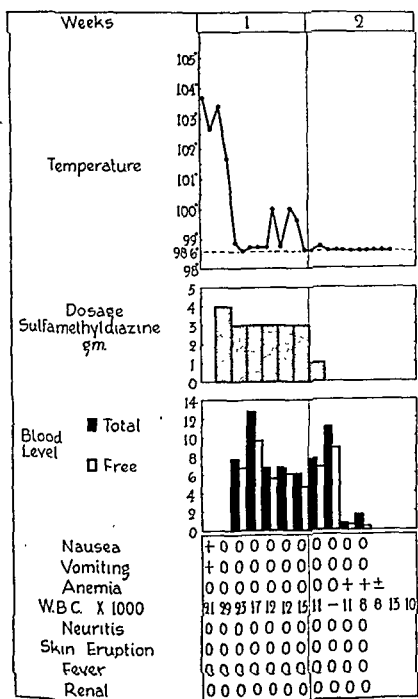


FIGURE 1. Chart of a Patient with Lobar Pneumonia (Type 7) Treated with Sulfamerazine.

holism. The blood culture on entry was positive for Type 12 pneumococcus. He developed an acute bacterial endocarditis and died with a terminal pneumococcal meningitis twenty-eight days after entry.

Lobar pneumonia—type undetermined. There were 17 adult patients presenting the typical findings of lobar pneumonia in whom no causative organism could be recovered from either the blood or the sputum. The average duration of treatment in these cases was six and a half days, and the average total dosage was 18 gm. Blood levels showed substantially the same range as those in the group of patients with pneumococcal lobar pneumonia.

Bronchopneumonia. Twenty-two patients with bronchopneumonia were treated with sulfamerazine. In 2 patients pneumococci were recovered from the sputum. In 20 patients no causative organism could be isolated from the blood or sputum. Sixteen of these patients were adults and 6 were children. All

an opportunity to treat 50 patients suffering from this disease with sulfamerazine. Although many of these patients were desperately ill, all recovered. This series of patients is to be reported in detail elsewhere. Figure 2 shows the chart of a patient with meningococcal meningitis who responded rapidly to treatment with sulfamerazine.

Two patients who had meningococcemia without meningitis were treated with sulfamerazine and recovered. One of these patients, through error, received only 2 gm. of the drug and yet made a complete recovery.

Hemolytic streptococcus meningitis. One patient, a six-year-old girl with meningitis caused by a beta-hemolytic streptococcus, was treated with sulfamerazine. During the course of scarlet fever she developed acute otitis media on the right side. Five weeks after the onset of the scarlet fever, a simple mastoidectomy was performed. Convalescence was uneventful until four weeks later, when the mastoidectomy incision was revised because of persistent drainage. The patient then remained well for seventeen days, at the end of which time there was a sudden rise in temperature to 102.6°F., accompanied by the appearance of the signs of acute otitis media on the left side. Two days later, drowsiness and marked rigidity of the neck appeared. Lumbar puncture revealed a purulent fluid from which beta-hemolytic streptococci were cultured. The blood culture was sterile. The patient was given 2.5 gm. of sodium sulfamerazine intravenously and placed on oral dosage. Forty-eight hours after the beginning of treatment she was asymptomatic. Recovery was complete.

Pneumococcal meningitis. One patient, a two-month-old boy with meningitis due to Type 7 pneumococcus, was treated with sulfamerazine. At the time treatment was begun the patient had been ill with fever for four days but had had meningeal signs for only one day. The initial response was favorable, the temperature returning to normal in four days and remaining normal for the next six days. Sulfamerazine was discontinued on the ninth day. Two days later, the temperature rose to 103°F. The drug was resumed and the patient was given sufficient specific antiserum to produce an excess of circulating antibodies in the blood. No improvement resulted, however, and death occurred forty-eight hours later. Autopsy revealed massive amounts of exudate about the base of the brain and over the cerebral hemispheres.

Other Infections

Erysipelas. Twenty-one adult patients with facial erysipelas were treated with sulfamerazine. These patients were all moderately to severely ill, although none had positive blood cultures. In 15 cases the admission temperature was 101°F. or higher, 6 patients having temperatures above 103°F. The dosage of sulfamerazine was 2 gm. initially, followed

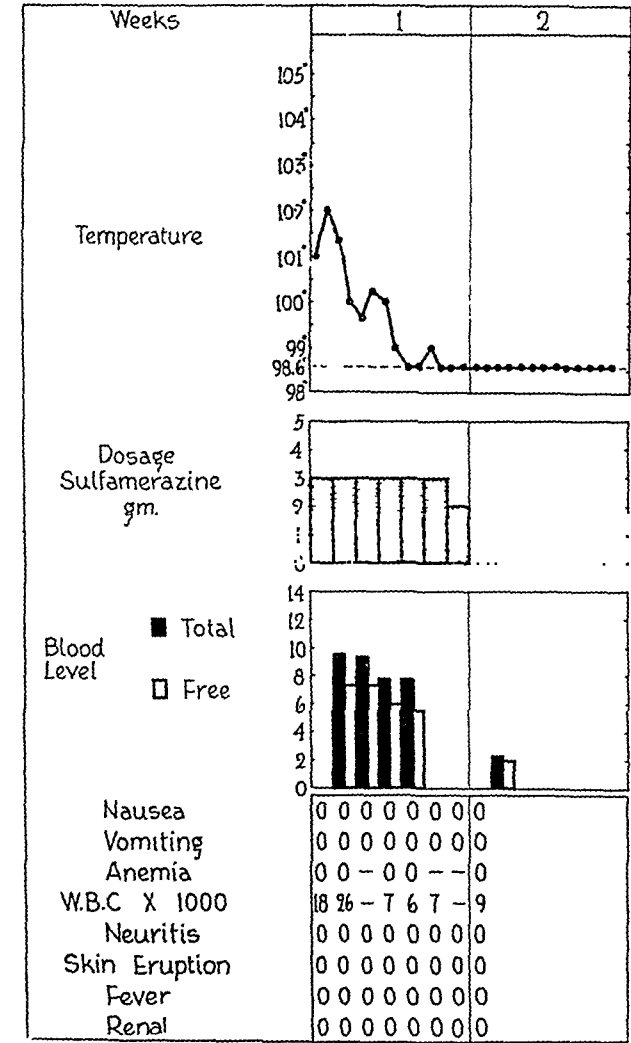


FIGURE 2. Chart of a Patient with Meningococcal Meningitis Who Responded Rapidly to Treatment with Sulfamerazine.

the patients recovered, although 2 of them relapsed and required a second course of chemotherapy before recovery was complete.

For the adult patients, the average duration of treatment was six days, and the average total dosage of sulfamerazine was 15 gm.

Primary atypical pneumonia of unknown etiology. Two patients who presented the characteristic features of this syndrome¹³ were treated with sulfamerazine. One received 12 gm. in five days, and the other 32 gm. in seven days. Both had blood levels of free sulfamerazine averaging 7 mg. per 100 cc. In neither case was there any evidence that sulfamerazine was beneficial.

Meningitis

Meningococcal meningitis. During the current epidemic of meningococcal meningitis, there has been

by 1 gm. every eight hours. In one case the maintenance dose was 0.5 gm. every eight hours. The average duration of treatment was four days, with an average total dosage of 12 gm.

The response to treatment with sulfamerazine was clear cut and extremely satisfactory (Fig. 3). All the patients recovered. Within twenty-four hours of the

Subacute bacterial endocarditis. Four patients with subacute bacterial endocarditis due to *Streptococcus viridans* superimposed on rheumatic valvulitis were treated with sulfamerazine. Three of them were treated late in the course of their disease for periods ranging from six to twenty-two days. Blood levels of free sulfamerazine between 6 and 9 mg. per 100 cc. were maintained. No significant improvement, either subjective or objective, occurred.

The fourth patient had been ill for only a month when therapy with sulfamerazine was instituted. On a dosage of 4 gm. a day she maintained a blood level that was consistently in the neighborhood of 15 mg. of free sulfamerazine per 100 cc. and 18 mg. of total sulfamerazine. After ten days of therapy, the blood cultures became sterile and remained sterile for twenty days. At the end of this time, they became positive again and remained so, although sulfamerazine was continued for another nineteen days, together with fever therapy and neosarsphenamine.

Infections of the urinary tract. Ten patients were treated with sulfamerazine for infections of the urinary tract — too small a number for statistical analysis. Of these, 4 had acute pyelonephritis. *Escherichia coli* alone was cultured from the urine of two patients and *Esch. coli* and *Staphylococcus aureus* from the urine of the other two. All four of these patients became asymptomatic on a daily dose of 3 gm. of sulfamerazine for periods varying from four to seventeen days. Only 1 patient was severely ill. This was a fifty-one-year-old man who had had dysuria for four weeks and chills and fever with back pain for one week before entry. On admission he was acutely ill; the temperature was 102°F., and there was marked tenderness in the left costovertebral angle. Blood and urine cultures were positive for *Esch. coli*. Therapy consisted of 3 gm. of sulfamerazine daily for eleven days. After seventy-two hours, the temperature did not rise above 100°F. and the patient felt greatly improved. At the end of a week, he was afebrile and asymptomatic.

Four patients were treated for acute cystitis. Three recovered completely after receiving sulfamerazine for periods varying from four to eight days. In the fourth case, therapy had to be discontinued after thirty-six hours because of vomiting, which was primarily due to causes other than chemotherapy.

One patient who was moderately ill with acute prostatitis and acute epididymitis following the use of an indwelling catheter made a satisfactory recovery in the course of ten days of therapy. One patient with chronic pyelonephritis was treated for three weeks without showing significant improvement. Urine cultures showed *Staph. aureus* and *Esch. coli*.

Acute otitis media. Forty patients with acute otitis media were treated with sulfamerazine. In 36 cases the otitis media was secondary to scarlet fever, in 2 to measles, and in the remaining 2 to nonspecific upper respiratory infections. Thirty-one patients

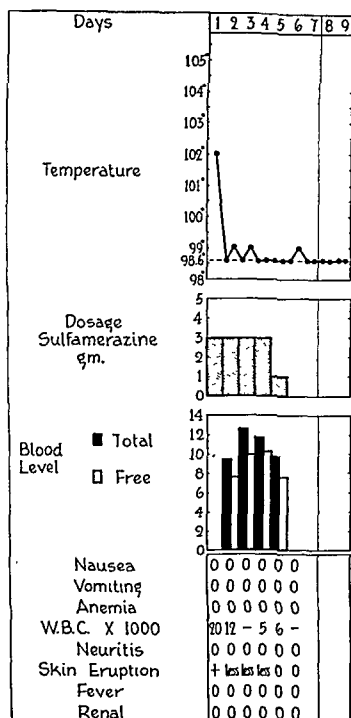


FIGURE 3. Chart Showing Prompt Response to Therapy with Sulfamerazine in a Patient with Facial Erysipelas.

beginning of therapy, all showed marked subjective improvement. In 10 patients defervescence had occurred within this period, and in 10 of the remaining 11 patients the temperature became normal by the end of forty-eight hours. The last patient had a marked acute cervical adenitis as well as facial erysipelas. The temperature did not return to normal until the end of the fifth day. No significant extension of the lesion took place in any case after therapy was instituted, and in the majority of cases resolution of the lesion was practically complete at the end of four days. The hospital stays varied from four to ten days, with an average of seven and a half days.

were children. The total dosage in this group was variable. The average blood levels maintained during the course of therapy varied from 3 to 17 mg. of free sulfamerazine per 100 cc. and from 5 to 20 mg. of total sulfamerazine.

Each patient was given a trial course of sulfamerazine for one week. If definite improvement, as evidenced by a decrease in the amount of discharge, was observed by the end of this time, the drug was continued until the ear became dry. If no improvement was observed, the drug was discontinued. The duration of treatment varied from three to eighteen days, with an average of seven days.

The results of treatment do not lend themselves well to evaluation, since no attempt was made to observe a control series. Of the 40 patients, 35 had an aural discharge either as the result of paracentesis or of spontaneous rupture of the tympanic membrane at the time sulfamerazine was started. In 22 (63 per cent) of these patients the ear became dry during treatment. In 13 (37 per cent) drainage persisted at the time sulfamerazine was discontinued. Six patients eventually required mastoidectomy.

Treatment was begun in 5 patients while the otitis was still in the catarrhal stage. In all these cases, the infection resolved without the occurrence of drainage.

Acute tonsillitis, peritonsillitis and cervical adenitis. This is another group of patients in which, because of the lack of adequate controls, satisfactory evaluation of results is not possible. Five patients with acute tonsillitis showed defervescence within twenty-four hours of the beginning of sulfamerazine therapy, and marked improvement in both local and constitutional signs by the end of forty-eight hours. Two patients with severe peritonsillitis showed a satisfactory response to therapy. Fever disappeared within forty-eight hours, and local signs had completely subsided by the end of five days. Two patients with severe cervical adenitis secondary to scarlet fever showed satisfactory resolution of the adenitis after seven and nine days of therapy, respectively.

Staphylococcal infections. In addition to the 3 patients with pyelonephritis due to staphylococci, 7 others suffering from staphylococcal infections were treated with sulfamerazine. Two of these patients had bacteremia due to a hemolytic *Staph. aureus*.

The first patient was a forty-five-year-old woman with monocytic leukemia who developed a persistent bacteremia seventeen days before her death. She received 3 gm. of sulfamerazine daily for two weeks, on which dosage she maintained an average blood level of 10 mg. of free sulfamerazine per 100 cc. The blood cultures remained positive, and no clinical improvement was detectable.

The second patient was an eighty-three-year-old man with arteriosclerotic heart disease and cardiac failure who developed a *Staph. aureus* bacteremia five days before death. It was at first thought that he

was suffering from a cystitis secondary to the use of an indwelling catheter. He was accordingly started on a dosage of 0.5 gm. of sulfamerazine every eight hours. When the blood culture was reported positive twenty-four hours before death, the dosage was increased to 1 gm. every eight hours. A blood culture taken shortly before death was still positive for *Staph. aureus*.

Two elderly diabetic women with early gangrene of the toes developed cellulitis of the lower extremities due to *Staph. aureus*. Sulfamerazine was given in one case for twenty-two days and in the other for twenty-five days. Both patients continued febrile, and although the infection did not show significant extension during therapy, neither did it show any tendency to resolve. Mid thigh amputation was eventually necessary in both cases.

Two patients with large abscesses due to *Staph. aureus*, one of the breast and the other of the buttock, were placed on sulfamerazine shortly before incision and drainage was performed. Both recovered uneventfully, but there is no evidence that sulfamerazine played any role in their recovery.

The last patient was a fifty-year-old man who had an undrained Brodie's abscess of the right femur that had developed two years previously following bacteremia due to *Staph. aureus*. For several days before the present entry he had been ill with spiking fever and painful induration of the soft tissues of the thigh. *Staph. aureus* was cultured from pus aspirated from the indurated area. Three grams of sulfamerazine was given daily for eight days, the blood level of free sulfamerazine being maintained consistently in the vicinity of 10 mg. per 100 cc. During therapy the temperature continued to spike as before, and the local lesion definitely increased in extent. Sulfamerazine was discontinued after eight days.

Acute sinusitis. Four patients with severe acute sinusitis received sulfamerazine. In 3, there was prompt and permanent improvement in both local and constitutional symptoms. The fourth patient was a ten-year-old girl who developed a severe right ethmoiditis during the course of scarlet fever. Treatment with sulfamerazine was not begun until the sinusitis had been present for five days. Despite adequate blood levels of the drug, she did not improve, and four days later surgical drainage was performed, following which recovery was uneventful.

Gonococcal urethritis. Only 1 patient suffered from a gonococcal infection was encountered during this study. This patient, a twenty-four-year-old man, had had an active urethritis for six weeks. Two courses of sulfathiazole and a course of local irrigations had not cleared the infection. The patient was hospitalized and put on complete bed rest for thirteen days, during which time he was given 45 gm. sulfamerazine. By the end of that time the discharge had ceased. Urethral smears and cultures were negative. When the patient was seen five weeks after discharge, there had been no recurrence.

In addition to the 239 cases that have been discussed, 39 additional patients were given sulfamerazine. In most of them the presence of an infection susceptible to the action of chemotherapy was suspected but never satisfactorily established. In the remainder, the use of multiple therapeutic measures made proper assessment of the role of sulfamerazine impossible and the therapeutic response could not be adequately evaluated. These patients, however, are included in the section on toxicity.

TOXIC REACTIONS

Excluding uncomplicated crystalluria, toxic reactions were observed in 70 (25 per cent) of the patients treated. For the most part, these reactions were mild and not of a character to jeopardize the patient's health or cause severe discomfort. The incidence of toxic manifestations in this series is somewhat higher than that reported by Clark et al.⁵ In Table 2 are summarized all the reactions observed in the present series. Included in the number of patients showing

TABLE 2. Toxic Reactions in 70 of 278 Patients Receiving Sulfamerazine.

	NO OF CASES	PERCENTAGE
Nausea	18	6.5
Vomiting	12	4.3
Headache	3	1.1
Psychosis	5	1.8
Anemia	3	1.1
Leukopenia (below 4000)	8	2.9
Granulocytopenia (below 50 per cent)	3	1.1
Crystalluria	60	21.5
Microscopic hematuria	20	7.2
Gross hematuria	2	0.7
Renal colic	2	0.7
Anuria	1	0.4
Drug rash	14	5.0
Drug fever	14	5.0
Joint pains	1	0.4
Conjunctivitis	1	0.4

crystalluria are 36 who showed uncomplicated crystalluria as the only manifestation of toxicity. These patients are not included in computation of toxicity for the whole series.

Nausea and vomiting. Eighteen patients (6 per cent) experienced nausea, and 12 of these vomited. The vomiting was never severe or protracted. It interfered with the continuance of oral therapy in only 1 patient, and in this case the vomiting was due primarily to causes other than chemotherapy.

Headache. Three patients complained of moderate headache that could reasonably be attributed to the use of sulfamerazine. In only 1 did the symptom persist throughout therapy.

Toxic psychosis. Five patients developed marked mental confusion that was presumably caused by sulfamerazine. In all the cases it came on within forty-eight hours after the first dose of drug and persisted until it was stopped. The blood levels were not unusually high in any case. All these patients were acutely ill with high fever at the time chemotherapy was started. In 4 cases there was a definite history of previous psychiatric abnormalities. The fifth patient was a senile woman of seventy-eight.

In all cases the mental confusion cleared completely one to three days after stopping the drug.

Anemia. A significant degree of anemia that could not be attributed to the underlying disease appeared in 3 patients during the course of therapy. In each case there was a gradual fall in the red-cell count and hemoglobin over a period of six to eight days. The average decrease in hemoglobin was 3 gm., and the red-cell count fell an average of 1,400,000. No cases of acute hemolytic anemia were encountered.

Leukopenia. The effect of sulfamerazine on the white blood cells deserves special mention. A fall in the leukocyte count to below 4000 was observed in 8 patients. In 4 cases, the fall occurred only after therapy lasting from fifteen to twenty-five days. Two of these patients showed a marked granulocytopenia, whereas in the other 2 the normal percentage of granulocytes was maintained. One of the patients showing granulocytopenia was reported to have developed a white-cell count of 2000 with 50 per cent neutrophils several weeks previously after five days of sulfadiazine therapy.

The 4 other patients showed leukocyte counts of less than 4000 cells after periods of therapy ranging from five to twelve days. Three of these showed no depression of the granulocytes. The fourth was a patient with monocytic leukemia who had shown only 1 or 2 per cent granulocytes for several weeks before sulfamerazine was started. Her total white-cell count at the time therapy was started was 126,000. By the ninth day of therapy it had gradually fallen to 3400. Sulfamerazine was continued for another six days, during which time the count fluctuated between 4000 and 8000. Two days after sulfamerazine was discontinued, it had risen to 20,000. Despite the marked changes in the total count, no significant changes in the differential count occurred, nor was there any detectable change in the course of the leukemia, which terminated fatally three days after treatment was stopped.

In all the above cases except the last, sulfamerazine was discontinued as soon as the leukopenia was discovered, and in 6 cases the white-cell count returned to normal a few days after chemotherapy was stopped. The seventh patient was an infant with pneumococcal meningitis who was moribund at the time the leukopenia developed and died shortly thereafter. The leukopenia in this case may well have been caused by the overwhelming infection and not by the drug.

Thirty-one other patients showed white-cell counts between 4000 and 4950 during therapy. These low counts were found mostly toward the end of the first week of sulfamerazine administration or during the early part of the second week. In 5 patients who had received the drug for periods ranging from five to twelve days, there was a moderate decrease in the percentage of granulocytes. In the other 26, the granulocytes showed no decrease. In 10 of these 31 patients sulfamerazine was continued for several

The evaluation of sulfamerazine as a chemotherapeutic agent may be approached most satisfactorily by comparing it with sulfadiazine. A comparison of these two compounds with respect to therapeutic efficiency can best be made from an analysis of the results obtained in the treatment of pneumococcal pneumonia, meningococcal menin-

gitis and erysipelas. The conditions encountered in these diseases are sufficiently standardized, and the experience with sulfadiazine in their treatment has been sufficiently uniform, to make the results the basis for a valid preliminary comparison.

Pneumococcal pneumonia. In pneumococcal pneumonia, the mortality rate of 9 per cent is of the same order as that reported by investigators using sulfadiazine (Table 3). The incidence of complications of pneumonia in the present series was likewise com-

Meningococcal meningitis. Fifty consecutive cases of meningococcal meningitis were treated with sulfamerazine without a death. In the first report on the use of sulfadiazine in this disease, Dingle, Thomas and Morton¹⁶ treated 13 cases, with 1 death. Subsequently, Hodes and Strong¹⁷ reported the treatment of 10 patients with no deaths, and Rundlett and her co-workers¹⁸ the treatment of 23 cases with no deaths. Feldman et al.¹⁹ had 2 deaths in 24 cases. It is clear that sulfamerazine is a potent and efficient

TABLE 3. Comparison of Mortality Rates in Pneumococcal Pneumonia Treated with Sulfamerazine and with Sulfadiazine.

	SULFAMERAZINE		SULFADIAZINE			
	FINLAND et al. ⁷	FINLAND et al. ⁸	FLIPPIN et al. ⁹	ENSWORTH et al. ¹⁰	BILLINGS and Wood ¹¹	DOWLING et al. ¹²
Number of cases	44	178	80	200	105	115
Mortality rate (per cent)	9	10.7	7.5	12.0	10.9	7.6

parable to those reported for the sulfadiazine-treated cases.^{7, 9, 10, 12} The rapidity of response to therapy is more difficult to compare. Fifty per cent of the patients who recovered without complications following sulfamerazine were afebrile at the end of forty-eight hours. Finland and his group⁷ reported that 75 per cent of their patients were essentially afebrile within thirty-six hours of the first dose of the drug. Dowling et al.¹² state that in 68 per cent of their cases the temperature was normal within forty-eight hours, whereas Flippin et al.⁹ reported the temperature to have become normal in 55 per cent of their patients by the end of forty-eight hours.

A comparison of the average total dose of sulfamerazine used in the patients with pneumococcal pneumonia who recovered with the average total doses used in the sulfadiazine-treated cases is of interest. The impression gained from the preliminary investigations of the absorption and excretion of sulfamerazine that a smaller total dosage would be required than with sulfadiazine was well borne out.

An average total dose of 20 gm. of sulfamerazine was administered to the patients who recovered. Finland and his associates^{7, 8} have reported average total doses of 42 gm. and 38 gm. of sulfadiazine for those recovering in two groups of patients. Flippin¹⁴ reported an average total dosage of 27 gm. It is of interest that Domm and others,¹⁵ in treating 25 patients with sodium sulfadiazine by the intravenous route alone, gave an average total dose of 20 gm.

From the foregoing analysis, it appears reasonable to conclude that in the treatment of pneumococcal pneumonia sulfamerazine shows an effectiveness similar to that of sulfadiazine. Furthermore, it appears that the total dosage necessary for adequate treatment of this disease is about one half to one third less than the amount of sulfadiazine ordinarily used.

agent in the treatment of meningococcal meningitis, equaling if not surpassing sulfadiazine.

Erysipelas. Twenty-one patients with erysipelas treated with sulfamerazine made prompt and complete recoveries. Finland and his colleagues^{7, 8} have reported a total of 64 cases of erysipelas treated with sulfadiazine with equally satisfactory results. In the present series, the average total dose of sulfamerazine was 12 gm., whereas in Finland's cases the average total dose of sulfadiazine was 27 gm. It appears, therefore, that in the treatment of erysipelas sulfamerazine equals sulfadiazine in efficiency, and that the average total dose of sulfamerazine is about half that of sulfadiazine.

Staphylococcal infections. The results obtained in the treatment of staphylococcal infections with sulfamerazine were not encouraging. The cases treated, however, were not of a type to afford a particularly fair trial for the drug. A greater experience will be necessary before an opinion can be formed about the effectiveness of sulfamerazine in infections caused by staphylococci.

Toxic reactions. A comparison of sulfamerazine with sulfadiazine on the basis of toxicity is also necessary. In Table 4 the toxic reactions to sulfadiazine that have been reported by several investigators are summarized and compared with those encountered after the use of sulfamerazine in the present series. It can be seen that the incidence of nausea and vomiting in the present series of cases was slightly higher than that usually reported for sulfadiazine. The number of patients developing a toxic psychosis approaches the average incidence of this reaction in the sulfadiazine-treated patients. The appearance of anemia in patients treated with sulfadiazine has been reported only in isolated cases. In the present series, 3 patients developed a mild anemia.

The appearance of leukopenia (a white-cell count below 4000) in 3 per cent of the patients treated with sulfamerazine constitutes a definitely higher incidence of this toxic reaction than has been reported for cases treated with sulfadiazine. Further significance may be attached to this finding when it is recalled that an additional 31 patients (11 per cent) showed a fall in the white-cell count to between 4000 and 5000. It appears, then, that sulfamerazine shows a distinctly greater tendency than does sulfadiazine to depress the white-cell count. Whether this property constitutes a serious drawback to the value of

SUMMARY AND CONCLUSIONS

The results of treatment with sulfamerazine patients are presented, together with the toxications manifested by this group and by 39 additional patients during the course of therapy. Sulfamerazine exhibited a therapeutic effect similar to that of sulfadiazine in the treatment of pneumococcal pneumonia, meningococcal meningitis and erysipelas. Sulfamerazine was clinically effective in doses that were on the average one half to one

TABLE 4. Comparative Incidence of Toxic Reactions With Sulfamerazine and With Sulfadiazine.

	SULFAMERAZINE		SULFADIAZINE					All Cases 1712
		FINLAND et al. ⁷	FINLAND et al. ⁸	FLIPPIN et al. ⁹	ENSWORTH et al. ¹⁰	DOWLING et al. ¹²	TREVETT et al. ²⁰	
Number of cases.....	278	446	460	200	239	137	230	
	%	%	%	%	%	%	%	
Nausea with or without vomiting.....	6.5	9.2	5.0	4.5		4.4	1.3	
Toxic psychosis.....	1.8		0.4	5.0		3.0	0.0	
Anemia.....	1.1	0.0	0.0		0.4	0.7	0.0	
Leukopenia (below 4000).....	2.9	2.0	0.7	1.5*	1.7	2.2	0.9	
Crystalluria.....	21.5	7.8	9.8	25.0				
Microscopic hematuria.....	7.2	0.4	4.3	4.0	2.5		1.7	
Gross hematuria.....	0.7	0.2	0.9	0.0	0.4			
Renal colic.....	0.7	0.2	0.9	0.0	0.4		0.9	
Anuria.....	0.4	0.2	0.2	0.0			0.0	
Fever or rash, or both.....	6.5	2.2	1.7	2.0	2.5	3.0	3.0	

*Below 5000.

sulfamerazine as a chemotherapeutic agent depends on the results of greater experience with the drug. So far, recovery from leukopenia has been prompt and without complication. In our own experience, leukopenia occurring in the first week has been of little consequence, since it frequently disappears even when the drug is continued. Crystalluria occurred with about the same frequency with both drugs. Microscopic hematuria showed a moderately higher incidence in the patients treated with sulfamerazine. Gross hematuria and renal colic occurred with about the same frequency with both drugs. From these figures, it may be gathered that despite theoretical considerations, sulfamerazine has about the same capacity for causing renal complications as has sulfadiazine. The incidence of rash and fever in this series is somewhat higher than the figure reported for sulfadiazine but is still not particularly striking in itself. In summary, it seems fair to say that in general the toxic reactions following the use of sulfamerazine are of about the same character and incidence as those following the use of sulfadiazine. Two exceptions should possibly be made to this statement: first, that sulfamerazine has a greater tendency to cause leukopenia than has sulfadiazine; and second, that the incidence of drug rash and drug fever may be somewhat higher with sulfamerazine. Further experience is necessary before these last points can be fully evaluated.

smaller than the amounts of sulfadiazine administered for similar conditions. Toxic reactions to sulfamerazine were in general of the same character and occurred with about the same frequency as those caused by sulfadiazine. The greater tendency for sulfamerazine to produce leukopenia and to cause drug rashes and drug fever constitutes a possible exception to this statement. It may be concluded that sulfamerazine is a valuable chemotherapeutic agent and a valuable addition to the sulfonamide derivatives already in general use.

We are indebted to Dr. William Feirer of Sharp and Doherty Company, Philadelphia, for supplying the sulfamerazine used in this study, to Miss Thelma Maxon and Miss Constance Haynes for technical assistance, and to the house officers of the Fifth and Sixth Medical Services (Boston University School of Medicine), Boston City Hospital, for their cooperation.

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ENCAPSULATED PLEURAL EFFUSION DUE TO HEART FAILURE*

A Report of Two Cases

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BALTIMORE

THE occurrence of encapsulated pleural transudation due to heart failure has been reported in the literature in less than 50 cases. The first case, observed by Helm¹ during 1912 and 1913 and proved by autopsy, was published five years later. This author made the observation that serial x-ray examinations of the chest showed marked changes. Sharply delineated shadows extending across a lung field were later demonstrated to have become so indistinct as to defy recognition had one not been acquainted with previous films. Fleischner,² in his report of 2 cases in 1926, confirmed Helm's observation that alterations in the x-ray shadows accompanying variations in the degree of heart failure. Stewart's³ case published in 1928 was followed by the reports of several other American authors.⁴⁻¹²

Because of the paucity of cases on record, the general impression has been that this condition is rare. The report of Bedford and Lovibond¹³ from England, however, indicates that encapsulated pleural effusions due to cardiac failure may be more frequent than recorded heretofore. In a series of 368 cases of heart failure, they found 136, or 35 per cent, with x-ray evidence of simple hydrothorax. Of these 136 cases, there were 11, or 8 per cent, with interlobar effusions.

CASE REPORTS

CASE 1. A 73-year-old, married Jewish woman (SH U-12502-1) was admitted on November 15, 1939, with an infection of the urinary tract. For several months prior to admission, she had experienced repeated attacks of angina pectoris, associated with weakness, dyspnea and cyanosis. The temperature on admission was 102°F. (rectal), the pulse 120, the respirations 38, and the blood pressure 128/68. The positive physical findings were limited to the heart and lungs. The chest was emphysematous without bony deformity. The respiratory excursions were equal on both sides. There was dullness on percussion over almost all of the right base, and over a small part of the left base, posteriorly. Medium moist rales were heard only at the right base posteriorly.

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teriorly. The trachea was not deviated. The apical impulse of the heart was palpable in the 5th interspace, 9.5 cm. to the left of the midsternal line. The heart was not considered to be enlarged. The heart sounds were of fairly good quality; the rhythm was regular, and there was a soft systolic apical murmur.

The anemia. for albuminous to blood 51 mg. per 100 cc.

The infection of the urinary tract responded favorably to sulfonamide therapy. During hospitalization the patient had a few attacks of weakness associated with an alteration in the quality of the heart sounds, but without a drop in blood pressure or a change in the cardiac rhythm. An x-ray film of the chest (Fig. 1) showed two distinct circular shadows in the right lower lung field, which were interpreted as interlobar effusions.

The patient was discharged improved after 5 weeks. She is still alive and quite well, but has refused to return to the hospital for physical examination and x-ray examination of the chest.

CASE 2. A 62-year-old, married Jewish grocery clerk (SH U-23500-1) was admitted on July 27, 1942, because of cough, dyspnea and a recent weight loss of 15 pounds. The cough had been productive of frothy white sputum. There had been no thoracic pain, wheezing, hemoptyses, chills or sweats. In 1921, the patient had spent 2 months in another hospital because of painful knees and ankles, which subsided with salicylate therapy. No abnormality of the heart was noted at that time.

On admission, the temperature was 102.4°F. (rectal), the pulse was 100, the respirations 28, and the blood pressure 110/70. The patient was well developed but showed evidence of recent loss of weight. He was dyspneic, orthopneic and cyanotic. The cervical neck veins were distended. The trachea was deviated to the right. The respiratory excursions on the right side were limited. Tactile fremitus was increased on the right and diminished on the left side. There was dullness on percussion in the left axillary region and over both bases posteriorly. Medium moist rales were heard in the right axilla and posteriorly over the right lower pulmonary field, extending up to the angle of the scapula. The precordium was visibly at cardiac impulse was 9.0 cm. to

There were no thrills, shocks regular and the heart sounds were of fair quality. A presystolic crescendo murmur was localized over the xiphoid process. The second pulmonic sound was markedly accentuated, and a protodiastolic gallop rhythm was audible at

§Reported through the courtesy of Dr. Samuel Wolman.

the apex. The liver and spleen were palpable 1 or 2 cm. below the costal margin and were not tender. There was no peripheral edema.

The admission hemogram revealed a mild hypochromic anemia with leukocytosis. The urine was essentially negative. A serologic test for syphilis was negative. The blood

was found. Following this procedure he ran a course characterized by severe dyspnea and a remittent fever. Digitalization effected temporary improvement. On the 9th hospital day, a left thoracentesis was performed and 1000 cc. of clear yellow fluid was removed. The specific gravity of the fluid was 1.010; a cell count revealed 10,000 red cells (probably



FIGURE 1. Anteroposterior and Lateral Views of the Chest in Case 1, Showing Encapsulated Interlobar Effusion.

sugar was 89 mg. per 100 cc., and the blood urea 67 mg. per 100 cc. Studies of the sputum for elastic tissue and for tubercle bacilli and other pathogenic organisms were negative.

An x-ray film of the chest (Fig. 2) taken the day after admission showed an ovoid, opaque shadow in the middle right

due to a trauma) and 300 white cells, with a predominance of mononuclear cells.

The thoracentesis was followed by temporary relief of the dyspnea, but the patient continued to go downhill, with increasing dyspnea, orthopnea, cyanosis, edema of the hands



FIGURE 2. Anteroposterior and Lateral Views of the Chest in Case 2, Showing Encapsulated Interlobar Effusion.

pulmonary field, with pleural thickening along the right base in the axillary line. There was a left pleural effusion. The roentgenologist's diagnosis was probable neoplasm with thickened pleura at the right base and a pleural effusion on the left side. The patient was bronchoscoped, but no tumor

and feet, stupor and, finally, pulmonary edema. On the 15th day, the temperature rose to 105°F. and the patient died.

Autopsy (performed 3½ hours after death). The right pleural cavity was practically obliterated by fibrous adhesions, and the left pleural cavity contained approximately

1100 cc. of clear, straw-colored fluid. The right lung was completely covered by fibrous adhesions. These were found to form a wall for a pocket of fluid situated posteriorly between the upper and lower lobes. Within this pocket, a band of fibrous adhesions extended from the upper to the lower lobe. Another pocket of fluid was found between the diaphragm and the diaphragmatic surface of the right lung. Foci of bronchopneumonia were found in the lower lobe of the right lung, and numerous small infarcts were present in all lobes. Pulmonary edema was marked. The heart was moderately enlarged. There was a rheumatic mitral stenosis associated with dilatation and hypertrophy of the left and right auricles and of the right ventricle. In addition, there was moderate coronary arteriosclerosis, and in association with this a healed infarct of the posterior wall of the left ventricle. The usual picture of chronic passive congestion was present in the liver and spleen.

COMMENT

The anatomy of the potential interlobar spaces and the characteristic roentgenogram of interlobar effusions have been described in a number of contributions.^{5, 11, 14} Suffice it to note that interlobar effusions are characterized by well-defined shadows along the interlobar septums, which may be circular, ovoid, band-shaped or wedge-shaped. It is generally agreed that in some cases a lateral film of the chest is helpful in differentiating this condition from carcinoma, cyst, gumma or abscess of the lung and from marginal pneumonia.

The original concept of the pathogenesis of interlobar effusions due to heart failure is reviewed in Austrian's⁷ article; namely, that with obliteration of the interpleural space due to antecedent infection, there is no other space available in which the effusion can localize. Anatomical investigation has borne out the fact that in some of these cases the interpleural space has been obliterated. In most cases, however, histories of previous pulmonary infections and of pleurisy have been lacking.

Stein and Schwedel⁹ offer an alternative explanation for the cases that show simple hydrothorax in addition to encapsulated effusions. They hold that with simple pleural effusions there may be an indentation at the interlobar fissure, with seepage of fluid from the general pleural cavity into the interlobar spaces. With repeated episodes of heart failure or in chronic cardiac failure — with hydrothorax, there may be organization of fibrin, resulting in pleural thickening. Such a process may go

on to the formation of adhesions between the parietal and visceral pleuras, with subsequent obliteration of the interpleural space. Fluid may then collect only in the interlobar spaces and become encapsulated.

Rigler,^{15, 16} in his x-ray studies of cases with simple pleural effusion, has demonstrated variations in the intensity of interlobar markings that can be altered by changing the position of the patient. He believes that such x-ray changes may be explained by the extension of fluid from the general pleural cavity into the interlobar spaces before encapsulation has taken place. With the deposition of fibrin and subsequent encapsulation of the interlobar effusion, however, changing the position of the patient does not alter the x-ray appearance of the shadow.

SUMMARY

Two cases of encapsulated pleural effusion in association with heart failure are reported.

The various concepts of the pathogenesis of interlobar effusion and the roentgenographic characteristics are reviewed.

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MEDICAL PROGRESS

PSYCHIATRY

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BOSTON

THE partially informed, and possibly gullible, layman often speaks with admiration and awe to the psychiatrist of the "wonderful new field" in which the latter works. The better-informed person, perhaps a physician who is not a psychiatrist, may smile a little wryly about the wonderful new field, thinking of a rather meager fulfillment of the supposed possibilities of psychiatry in regard to progress.

The undertaking of personality problems — mental and emotional disabilities — by a certain branch of medicine does not justify the conclusion that that department of medicine has failed in its intention if permanent cures are not effected in the majority of cases. Psychiatry is attempting to do all that can be done, often against impossible odds. The progress is not disheartening if this is considered.

Neuropsychiatry is much better organized in this war than in the last for responding to the demands made of it — namely, primary elimination of the men unfit for military service, secondary elimination in the early stages of training and treatment of those who break down in combat areas. Shock treatment for the psychoses, although it has not reorganized defective material into permanently healthy material, has hastened recovery and has lessened immediate suffering. Attempts to introduce knowledge of the principles of mental hygiene and an understanding of emotional reactions into elementary education have continued.

SHOCK THERAPY

Insulin and metrazol have now been used in this country over a long enough period — more than seven years — for the treatment of schizophrenia to permit a fairly reasonable evaluation of their effectiveness. Because of the danger of vertebral fracture, metrazol is used less frequently or is employed in combination with insulin.¹ Insulin has proved its value in that it so often shortens the duration of the psychotic attack. It cannot be counted on to prevent relapse.

Some investigators still report that the insulin-shock method results in no higher rate of recovery than is obtained with the more conservative types of treatment. Gottlieb and Huston,² for example, found in the Iowa State Psychopathic Hospital that 66 patients treated with insulin showed no better remission rate than did 132 patients who did not receive pharmacologic treatment. On the other

hand, Bond and Rivers,³ at the Pennsylvania Hospital, consider insulin therapy justified, "with an immediate recovery rate five times that of control cases . . . and with a long-distance recovery rate twice that of controls." Their investigations cover a seven-year period.

Of the drastic measures for treatment of the psychoses, attention has been centered in the past few years on electric shock. As with insulin and metrazol, no promise of permanent cure is offered, but immediately favorable results have frequently occurred. Electric shock has been most successful in cases of depression, both of the manic-depressive and the involutional types. Some workers have reported amelioration in schizophrenia, but in general it is the depressions that have given the best response.

In a follow-up study on 126 patients treated with metrazol and 144 patients treated by electric shock, cases of dementia praecox, manic-depressive and involutional psychosis and psychoneurosis, Pacella and Barrera⁴ say that their statistics "suggest that possibly the electric shock method may be slightly more efficacious, at least in so far as the immediate results are concerned." The metrazol cases were followed for eighteen to twenty-four months and the electric shock cases for six to fifteen months after treatment.

These workers found the results of both types of treatment rather discouraging in the psychoneurotic cases. They consider convulsive treatment of undoubted, great value in the effective psychoses. It is interesting that in the schizophrenic patients only those who had strong affective components, principally of a depressive kind, showed substantial improvement or complete remission.

During a year and a half Reznikoff⁵ treated 100 schizophrenic patients with electric shock. He found a pronounced tendency to relapse, as he had previously found in 100 schizophrenic patients treated with metrazol. He states that electric shock is preferable to metrazol because of the amnesia for the treatment, less fear and anxiety and painless shock in the former.

In regard to fear of electric-shock treatment, Myerson⁶ says:

It is safe to say that the statement made in the literature that there is no fear of the treatment is not correct; there is less than with metrazol shock, and often enough the individual treatment is not at all remembered. In the relatively sane patients, the whole matter of repairing to a hospital, of becoming unconscious and of a period of agitation and loss of memory afterward becomes linked up

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with the idea of treatment, and a definite association fear of the treatment develops. In the markedly psychotic cases, no such fear seems to be experienced.

Favorable response to electric shock, if it occurs, usually follows a comparatively small number of treatments. Sulzbach, Tillotson et al.⁷ have given only two to six convulsive shocks in all their successful cases and have seen no impressive results if the latter have not been obvious after ten treatments. They give treatments twice, rarely three times, a week. Myerson,⁸ in a series of 120 cases, gave seven or less shocks to each patient.

Outpatient or extramural electric-shock therapy has proved practicable in certain cases. Wender, Balser and Beres⁹ report a series of 40 cases so treated. In choosing such procedure, both the psychiatrist and the patient's family have to keep in mind the danger of suicide. The advantages are the preclusion of the expense of hospitalization and of the dread or prejudice of certain patients or their families in regard to hospital admission and care.

Popular and effective, at least temporarily, as electric shock is, it should, of course, not be used indiscriminately. The physical condition of the patient, especially that of his heart and blood vessels, and his age must be considered. It is surprising, however, how well some elderly patients have withstood the rigors of treatment. If the mental illness is particularly severe and intractable over a long period of time, it is fair to estimate the advantages of this treatment against its disadvantages. Evans⁹ gave convulsive treatment, either by electric shock or by metrazol, to a series of patients over fifty years of age, and in a report on the first 50 consecutive cases claims in 40 of them either recovery or enough improvement to permit discharge of the patients to their homes.

Although experimental work on animals has revealed some brain damage, chiefly small hemorrhages, in connection with electric shock, there seems to be no evidence that serious or permanent injury of any disabling degree occurs in the brains of human beings. The confusion and loss of memory, which are typical, are apparently only of a temporary nature.⁶

WAR PSYCHIATRY

The literature, in both neuropsychiatric and general medical journals, is in large proportion composed of an unending number of articles on the psychiatric aspects of war. This is not overemphasis, since such a considerable percentage of the casualties in combat areas alone, roughly 30 per cent, are of a psychiatric nature.

The Army, and to a less extent the Navy, in this country, from the inauguration of required service in the armed forces during the present war, have been alert to the fact that not every man who is physically well and able will make a satisfactory member of the forces. With their knowledge of

psychiatric casualties that occurred in World War I, they have attempted and are attempting to screen out or eliminate before induction the men who seem likely to break down nervously under the circumstances of training and combat. This is no simple undertaking.

The problem centers on this question: With the supposition that an adequate history is at hand for each man examined, if there are data indicating nervous or emotional instability in the past or at present, what are the definitions or interpretations that will give the examining physician sound guidance for accepting or rejecting the man? There is no clarifying answer. In the first place, adequate histories have seldom been obtained in the cases in which they would be most valuable, largely because psychiatric social service has only recently been established in most induction centers. In the second place, psychiatric knowledge and insight do not go to the extent of predicting unfailingly and exactly what degrees and kinds of nervous instability should exclude a man from service.

It is generally agreed that a history of psychotic attacks, long-standing neurotic reactions, — even though only slightly disabling in civilian life, — definite psychopathic tendencies, epilepsy and chronic alcoholism are reasons for rejection. Yet Bigelow¹⁰ has observed that some men with certain neurotic tendencies, anxiety states, conversion mechanisms and hypochondriacal complaints have been successful in military aviation. He proposes that flying may be a symbolic solution of their neurotic conflicts. It should be remembered that in the last war many a neurotic did well as an aviator.

There are, of course, in other branches of the service many men with neurotic tendencies who so far are doing well.¹¹ Whether or not they will later break down may depend on the kind of strain to which they are subjected.

From their experience in a naval hospital, Stearns and Schwab¹² conclude that the Navy has in the past not given sufficient attention to the importance of examining recruits thoroughly enough to exclude undesirable men. They say: "Our unmistakable conclusion is that the military service cannot absorb successfully large numbers of persons who are unable to get along in civilian life. These men should be rejected at the recruiting or . . . induction center."

The presence of a particular neurotic trait is not estimated to be so important as its severity or intensity. Also, the number of traits present in the personality rather than the existence of any one trait is thought by some to be the critical factor. Referring to work done at the Walter Reed General Hospital, Porter¹³ lists fifteen attributes the presence or absence of which are determined in the histories of patients diagnosed as having psychoneurosis or a constitutional psychopathic state. These are as follows:

(1) Bed-wetting beyond four years of age. (2) Thumbsucking or nail-biting beyond six years of age. (3) Failure to engage in competitive games involving risk of injury. (4) Tantrums in childhood. (5) Abnormal shyness or sensitiveness. (6) Preference of playing alone. (7) Repeated grades, difficulty with teachers, chronic truancy in school record. (8) Abnormal fears, such as lightning, dark, bogeyman. (9) Shunning of girls after puberty. (10) Faints. (11) Excessive autonomic system reactions to emotion: tremor, abnormal sweating, tachycardia, etc. (12) Sulkeness under discipline. (13) Abnormal attachment to mother after puberty. (14) Stammering. (15) Obsessional traits.

Porter explains that he and his colleagues believe that the presence of four significant traits is not uncommon in persons who have not become serious military problems, but that the presence of six or more should cause one to prognosticate a probable breakdown under stress. The same type of analysis has been interestingly and cautiously written about by Lewis and Slater.¹³ They dealt with 300 soldiers who were hospitalized for neurotic illness. One hundred and fifty of these were returned to service and were still on duty some months later. The other 150 were discharged. The authors advance the theory that the fewer psychoneurotic attributes the soldier has, the more likely it is that he will remain in the service. They point out, however, that the intensity and quality of the individual attributes have importance in prognosis.

Showing the significance of the relation between a history of nervous instability and later incapacity, Rosenberg and Lambert,¹⁴ in a study of 200 consecutive cases discharged from the Army at Camp Lee, Virginia, found that 100 per cent had symptoms prior to induction. Eighty-two and a half per cent had had symptoms for at least one year before induction, and a little more than 50 per cent had prominent symptoms for more than five years. The authors believe that the majority of these psychiatric casualties could have been eliminated at the induction board if relatively simple social service data had been made available. Gowan,¹⁵ in writing of nervous breakdowns in military service, says that one half to two thirds of the men with such disturbances show definite predisposition.

There are limits of endurance beyond which the strongest and sturdiest of constitutions cannot go without developing psychiatric disabilities. This is well presented by Smith¹⁶ in his description of the casualties among the Marines who fought at Guadalcanal. On the other hand, how remarkably well balanced a group of men can remain in the face of acute but not prolonged horror is depicted by Hogan¹⁷ in his account of the behavior of the crew of the U.S.S. *Wasp* when and after it was torpedoed and sunk.

Disturbing as may be the picture of such a large percentage of psychiatric illness as is occurring in the present war, the military services have become more and more cognizant of the necessity of eliminating, salvaging and educating. The replacement training centers are paying more attention to the organization of neuropsychiatric service, and the

attempt is being made to observe each man closely enough to prevent his leaving the center unless he is judged as fit for line duty. The men who are not so estimated are placed where they can best be used unless it seems obvious that they must be given certificates of disability discharge.^{18, 19}

It is incontrovertible that morale or idealism of some kind shares importance with physical or mechanical factors in determining how well an army, or any other group of men combined for action, does its job. The criticism is heard frequently that the men in the Army and Navy do not know what they are fighting for. Somewhat belatedly and not yet thoroughly enough, the military services are recognizing the extreme importance of training and education beyond the limits of a military manual.

As an example of how effective education in this direction can be, Cohen's²⁰ experiment with a prophylactic mental-hygiene discipline is fascinating, especially to the uninitiated. He was given permission to conduct three series of experiments, involving over 2000 trainees, at two different replacement training centers. The men were divided primarily into two groups, the experimental and the control. These were split secondarily into three groups who were given a number of mental-hygiene talks as part of the training program and three groups who were not given such talks.

The talks covered the following subjects: natural civilian resentments to Army life; regimentation; fear; and a résumé of all adjustment factors. From the day on which the talks began until basic training was completed a record was kept of all sick calls and hospitalizations. Following are the relevant statistics:

First Experiment

Sick calls for psychosomatic symptoms:

Experimental group, 8; control group, 23.

Hospital days for psychosomatic symptoms:

Experimental group, 4; control group, 47.

Second Experiment

Sick calls for psychosomatic symptoms:

Experimental group, 5; control group, 38.

Hospital days for psychosomatic symptoms:

Experimental group, 0; control group, 18.

Third Experiment

Sick calls for psychosomatic symptoms:

Experimental group, 6; control group, 28.

Hospital days for psychosomatic symptoms:

Experimental group, 0; control group, 17.

Promoting and maintaining mental health depends only in part on talks by an instructor. How it works is nicely illustrated in the story of Carlson's Raiders. These 1000 men fought on Guadalcanal and stormed Makin Island. During their exploits only one of them suffered traumatic war neurosis. *Fortune*, in its issue of December, 1943, gives a good description of their integrity and of Lieutenant Colonel Evans F. Carlson's understanding of human needs. Before each raid or attack Carlson discussed with

his men plans, means and reasons. Afterward, causes of failures or successes were also discussed. Quoting from *Fortune*:

Carlson believes that because he prepared the men for what they might expect; because he considered their opinions and feelings; because they were convinced he would never sacrifice a man needlessly; because he provided an outlet for terror and tension; because his men understood what they were fighting for; because the Raiders trusted him implicitly — they suffered virtually no psychiatric casualties.

In the combat areas and in the advanced mobile base hospitals, psychiatry is doing what it can under the circumstances. It hardly needs to be written again that, at least as concerns the health of the individual, treatment should be instituted as soon as possible after symptoms first appear and as near as possible to the geographic point of origin. Under the stress and strain of battle or attack, the first and quick and unwise reaction of some men — unwise from the point of view of future mental health — is to retreat as far as they can from the danger. There is a nice point here, for the mental integrity of some will be preserved only by complete retreat, whereas others underestimate their powers of resistance, just as some people have an overawareness of pain. The experienced and wise psychiatrist, or intuitive line officer, has to make the decision concerning the individual's potentialities for recovery.

The farther away from zones of danger the psychiatric casualty is removed the greater is his resistance to returning, and the more likely is resistance to be manifested by a continuance of his symptoms. Halloran and Farrell²¹ write that the experience of the British in finding that prolonged rest, induced by sedatives if necessary, good food and reassurance given near the front return to duty 70 to 80 per cent of men with acute combat neuroses has been confirmed in American troops.

According to Rome,²² group psychotherapy has been found expedient and efficient in certain advanced mobile base hospitals. It is difficult to imagine that there is much opportunity for psycho-

therapy in most combat areas, and it is known that in many such areas it is possible only to classify and evacuate. As in civilian group psychotherapy, there is benefit for the individual in appreciating that he is not alone in the kind of disability that he might otherwise look on as stigmatizing. As Rome says, "In a group, security is gained by a mutual pooling of insecurity."

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MASSACHUSETTS MEDICAL SOCIETY

PROCEEDINGS OF THE COUNCIL

Stated Meeting, February 2, 1944

THE Council of the Massachusetts Medical Society met at John Ware Hall, 8 Fenway, Boston, on Wednesday, February 2, 1944. The meeting was called to order at 10:00 a.m. by Dr. Roger I. Lee, Suffolk, president of the Society. There were 218 councilors present (Appendix No. 1).

The Secretary offered the record of the last meeting as published in the *New England Journal of Medicine*, issue of November 25, 1943.

Dr. John B. Hall, Norfolk, moved its approval. This motion was seconded by a councilor, and it was so ordered by vote of the Council.

REPORT OF AUDITING COMMITTEE

The report (Appendix No. 2) was presented by the chairman, Dr. Fritz B. Talbot, Suffolk.

Dr. David Cheever, Suffolk, moved that the report be accepted and placed on file. This motion was seconded by Dr. Albert A. Hornor, Suffolk, and it was so ordered by vote of the Council.

REPORT OF TREASURER

This report (Appendix No. 3) was offered by Dr. Eliot Hubbard, Jr., treasurer.

He said that the revenues of the Society for the year 1943 were \$7175.36 less than in 1942 and that this was largely explained by reason of the Society's policy of remitting the dues of those of its members who were in the services of the Nation.

He said that, under the advice of investment counsel, the yield of the General Fund had increased from 1.90 to 2.40 per cent and that of the Building Fund from 1.90 to 2.95 per cent, the total of the latter fund being \$66,566.69. He added that the total expenses for 1943 were \$33,133.02, as compared with total expenses of \$48,680.85 for 1942. The Society ended the year 1943, he concluded, with total assets of \$250,385.47.

It was moved by Dr. Hornor that the report be accepted with thanks. This motion was seconded by Dr. Cheever.

Dr. Carl Bearse, Norfolk, thought that the advance sheets distributed by the Treasurer should show the investments in more detail. Dr. Hubbard replied that he would be glad to supply such information if it was the councilor's wish.

The motion was adopted by vote of the Council.

REPORT OF EXECUTIVE COMMITTEE OF THE COUNCIL

The report was offered by the Secretary.

He spoke of the activities of the Committee Appointed to Consult with Representatives of the Other New England State Medical Societies Regarding

the Wagner-Murray-Dingell Bill. He particularly referred to a statement prepared by an informal group of physicians from the six New England states and added that the Executive Committee of the Council authorized the President and Secretary, in the name of the Massachusetts Medical Society, to send this statement in the form of an open letter to the Massachusetts representatives in the Congress of the United States.

The Secretary called the councilors' attention to the fact that this statement appeared in the advance sheets of information and that the statement itself would be presented later in the meeting as part of the report of this special committee.

The Secretary spoke of a memorandum received on December 23, 1943, from the Office of the Surgeon General of the United States Army, which stated in part, "This office will no longer recommend the appointment of graduates of Middlesex College of Medicine as commissioned officers in the Medical Corps, Army of the United States." He also referred to an article printed in the *Boston Herald*, issue of December 22, 1943, in which C. Ruggles Smith was quoted as saying that the probable reason for this action on the part of the Surgeon General was pressure from the American Medical Association. The Secretary spoke of a letter received from Dr. Olin West, secretary of the American Medical Association, in which any such activity on the part of this Association was denied.

The committee reviewed the reports of the Committee on Finance and the Postwar Loan-Fund Committee and approved both, recommending that certain parts of the report of the Committee on Finance be clarified.

The committee reviewed the report of the Committee on Cancer and noted that this committee was not in accord regarding its recommendations to the Council anent certain new regulations issued by the Massachusetts Department of Public Health for the direction of state-aided cancer clinics. It further noted that the majority of the committee recommended that the regulations be approved pending a six months' trial and that from this view the minority dissented. The committee referred the report back to the Committee on Cancer with certain memoranda originating in the Massachusetts Department of Public Health and supplied by Dr. Elmer S. Bagnall, president-elect.

The report acknowledged the receipt by the committee of a letter from Dr. Sidney C. Wiggin in which the latter requested that there be set up in the Massachusetts Medical Society a Section on

Anesthesiology. The Secretary reported that the committee recommended adversely in this matter, and moved the adoption of this recommendation. The motion was seconded by a councilor.

Dr. William A. R. Chapin, Hampden, said that there were many reasonable arguments advanced in Springfield in favor of the establishment of such a section and that it was a pity that there was not someone present to direct the debate in this direction. He added that he was sorry to see the matter go by default. Dr. Peirce H. Leavitt, Plymouth, expressing a similar viewpoint, said that if the anesthesiologists had the ambition to establish a Section on Anesthesiology they should be given the opportunity to go ahead. The Council, on a show of hands, adopted the recommendation of the committee.

The report referred to a communication from the Michigan State Medical Society in which the latter urged that the Massachusetts delegates to the House of Delegates of the American Medical Association be instructed to support a resolution calling for the establishment of an information bureau in Washington, D. C. The Secretary said that the committee recommended that this matter be left, without instruction, in the hands of the Massachusetts representatives in the House of Delegates, and moved the adoption of this recommendation. The motion was seconded by Dr. Charles C. Lund, Suffolk. Dr. Hyman Morrison, Norfolk, asked that the resolution be read. At the request of the President, the Secretary said that this resolution appeared on pages 17 and 18 of the advance sheets of information. The Secretary added that, when a similar matter was before the Council last May, the Massachusetts representatives were sent to the meeting of the House of Delegates uninstructed and that, as an observer at the meeting, the wisdom of this action was very apparent to him. The recommendation was adopted by vote of the Council.

The report spoke of certain appointments that had been made by the President since the last meeting of the Council and of their approval by the committee.

The Secretary moved the adoption of the report as a whole. This motion was seconded by a councilor, and it was so ordered by vote of the Council.

REPORTS OF COMMITTEES

Committee on Publications — Dr. Richard M. Smith, Suffolk, chairman.

The report (Appendix No. 4) was offered by the chairman, who in glowing terms spoke of the work of the editor, Dr. Robert N. Nye. He added that, under the latter's management, the *Journal* had become one of the outstanding medical publications in this country.

The report said that the total number of subscriptions as of December 30, 1943, was 11,909 plus 347 copies sent once each month to the members of

the New Hampshire Medical Society and that the outside subscriptions had been greatly increased, with the result that, although there had been many cancellations during the year, the net increase was 2704.

The report said that the financial operations of the *Journal* for the year had been very satisfactory, the net loss being \$5,852, as compared with a net loss of \$17,550 in 1942.

The report spoke of the employment of a new printer who took over on January 1, 1944, and said that this had been made necessary for many reasons.

The shortage of paper, the report continued, represented a problem that was being met in several ways. In respect to this matter the report went on to say that it may be necessary to cut the weight of the paper or the pagination or both.

Seventy-seven per cent of the papers submitted for publication were accepted.

The report spoke of the increase in the routine office work during the year and pointed out that the clerical work required by the officers and various committees of the Society had demanded more and more of the time of the office staff. To Miss Davies and her assistants the report gave unstinted praise for the handling of the work.

Dr. Smith moved the adoption of this report. The motion was seconded by a councilor.

Dr. Lee commented on the excellence of the report and said that with its adoption should go the grateful thanks of the Council. This motion was adopted by vote of the Council.

Committee on Arrangements — Dr. Gordon M. Morrison, Middlesex South, chairman.

Dr. Roy J. Heffernan, Norfolk, a member of the committee, announced, in Dr. Morrison's absence, that the committee had no report.

Committee on Ethics and Discipline — Dr. Ralph R. Stratton, Middlesex East, chairman.

No report.

Committee on Medical Education — Dr. Robert T. Monroe, Norfolk, chairman.

No report.

Committee on Membership — Dr. Harlan F. Newton, Suffolk, chairman.

No report.

Committee on Public Health — Dr. Francis P. Denny, Norfolk, chairman.

No report.

Committee on Medical Defense — Dr. Arthur W. Allen, Suffolk, chairman.

No report.

Committee on Society Headquarters — Dr. William H. Robey, Suffolk, chairman.

No report.

Committee on Finance — Dr. Francis C. Hall, Suffolk, chairman.

Dr. Hall called the councilors' attention to the committee's report (Appendix No. 5) as printed in the advance sheets of information beginning on page 3.

Dr. Hall moved the acceptance of the report. This was seconded by a councilor, and it was so ordered by vote of the Council.

Dr. Hall moved the adoption of the budget for 1944. This motion was seconded by a councilor.

Dr. Lester M. Felton, Worcester, spoke of a communication that he believed Dr. Brainard F. Conley had sent to Dr. Hall. Dr. Hall expressed his thanks to Dr. Felton for this reminder. The letter, Dr. Hall said, was to the effect that, whereas the Committee on Legislation had asked for \$100 originally, it was apparent that, because of national legislative matters, the committee would need a total of \$2000.

Dr. Hall moved, as an amendment to his original motion to adopt the budget as recorded in the advance sheets, that the sum of \$1900 be added to that which had been allowed the Committee on Legislation. This amendment was seconded by Dr. Felton.

Dr. George Leonard Schadt, Hampden, asked if the duties of the Committee on Legislation concerned this committee with national legislative matters. He was answered in the affirmative by the chair, who read Section 4 of Chapter VII of the by-laws. The motion as amended was adopted by vote of the Council.

Committee on Industrial Health — Dr. Dwight O'Hara, Middlesex South, chairman.

No report.

Massachusetts Committee on Procurement and Assignment — Dr. Reginald Fitz, chairman.

This report was offered as a courtesy to the Massachusetts Medical Society.

The report (Appendix No. 6), which was read by Dr. Fitz, stated that half the members of the Society less than forty-five years of age and two thirds of the members thirty-eight years old and younger were in active military service and that it was difficult to perceive how many more practicing physicians could be withdrawn without resulting in serious difficulty in the matter of the medical care of the civilian population.

The report spoke of the decision of the Surgeon General to no longer recommend the commissioning in the medical corps of graduates of a certain school and said that many of the young men affected by this decision were continuing to serve as residents and interns in hospitals badly needing them and that others had opened offices in areas claiming to need physicians. The report added that few, if any, had been drafted by Selective Service as privates.

The report spoke of the 9-9-9 plan for interns and residents.

Having in mind the influenza epidemic of twenty-five years ago, the report spoke of plans that were being jointly worked out with the War Participation Committee of the Massachusetts Medical Society, by which a type of emergency service could be established in the Commonwealth.

Dr. Fitz moved the acceptance of the report. This motion was seconded by a councilor, and it was so ordered by vote of the Council.

Committee on Public Relations — Dr. Albert A. Hornor, Suffolk, secretary.

Dr. Hornor reported as follows:

The committee met on December 15, 1943, at the Harvard Club and in addition to the president, president-elect, vice-president and secretary of the Society, there were representatives of twelve district societies.

The minutes of the last meeting were approved as distributed to members of the committee.

The report of the committee invited to sit with the Advisory Council of the Committee on Unemployment and Social Security for the Commonwealth of Massachusetts was presented as a progress report and discussed by all members present. It was duly moved and seconded and finally passed by unanimous vote that the Committee on Public Relations endorse and continue study, by subcommittee, of plans for sickness and indemnity insurance as presented before the above-named committee.

A progress report was received from the subcommittee to look into the possibility of better publicity for the Massachusetts Medical Society. The Committee on Public Relations voted unanimously in favor of a study for means of public education regarding the Massachusetts Medical Society by its subcommittee on publicity.

The Committee on Public Relations was designated, by President Lee, as the committee of the Society to function with the Council on Medical Service and Public Relations of the American Medical Association.

The formulary of drugs for recipients of public welfare, as published by the Department of Public Welfare, was discussed and referred to the Subcommittee on Tax-Supported Medical Care for study and appropriate report.

Dr. Hornor moved the acceptance of the report. This motion was seconded by a councilor, and it was so ordered by vote of the Council.

Subcommittee to Meet With the Medical Advisory Committee of the Industrial Accident Board —

Dr. Daniel J. Ellison, Middlesex North, chairman.

No report.

Subcommittee on Tax-Supported Medical Care —

Dr. Elmer S. Bagnall, Essex North, chairman.

Dr. Bagnall reported as follows:

To this subcommittee of the Committee on Public Relations was referred the matter of the *Formulary* at the first meeting of the Committee on Public Relations. Our report has not had a chance to be reviewed by the Committee on Public Relations and unless the Council desires otherwise, we think that it should wait until the Committee on Public Relations receives it.

Dr. Lee announced that Dr. Bagnall's report was accepted as a report of progress.

Subcommittee on Postpayment Medical Care (Bank Plan) — Dr. Elmer S. Bagnall, Essex North, chairman.

No report.

Subcommittee Concerned With Prepayment Medical-Care Costs Insurance — Dr. James C. McCann, Worcester, chairman.

Dr. McCann reported as follows:

I shall make a brief statement with respect to the present status of the corporation. At the last meeting of the Council we anticipated an enrollment of 15,000 subscribers by the first of the year. Today, the enrollment is 25,000, which is probably the most satisfactory response under the restricted program we offer — surgical-obstetrical benefits — that has been experienced by any of the states except Michigan, which has always had a most unusual experience.

Regarding the financial condition of the corporation, as we had anticipated in the last report, all the organizational expenses and current expenses have been taken care of, and we are operating in the black, and it looks as if during the next year a satisfactory surplus will begin to appear on the books. This is in addition to a rather rigid requirement of placing away a reserve of 25 per cent, as required by the Commissioner of Insurance.

With reference to the accumulation of reserves, the Board of Directors has already begun to discuss an extension of the basic contract to include medical care in the hospital. This, of course, would be much to our advantage in any new program. The control of this matter is also in the hands of the Department of Insurance in so far as they will require a satisfactory financial condition before we make this extension. In conversation with the deputies in the office of the Department of Insurance, they agreed to review our rates as of June and to make recommendations to us, and also to examine any plan that we may suggest for extending the benefits.

The relations of the corporation with the profession have so far been eminently satisfactory. In the office we are quite conscious of the delay in the handling of the reports from the profession and in making the final settlement of accounts; but this is an unavoidable situation until the administrative forces in the office become acquainted with the entirely new matter of medical problems as compared with the usual hospital problems. All along the way steps are being taken to eliminate such problems as delay in the handling of accounts, and I think that during the next year the members of the profession will find that matters will be handled in an increasingly satisfactory manner — at least that is our hope.

This is just an informal report, and I move that it be accepted as such.

Dr. McCann's report was accepted as a report of progress.

Committee on Legislation — Dr. Brainard F. Conley, Middlesex South, chairman.

The report, which was offered by Dr. Lester M. Felton, Worcester, is as follows:

Since the last meeting of the Council there have been four executive meetings of the Executive Committee of the latter group with the Legislative Committee of the Massachusetts State Pharmaceutical Association.

There has been established full, active co-operation between the druggists and the physicians of Massachusetts on matters of legislative interest to both professions.

The Massachusetts State Pharmaceutical Association has issued, at a small expense, a great amount of literature to the public through the drugstores of the State. This particular literature has to do with the dangerous aspects of the pending Wagner-Murray-Dingell Bill. On February 9 this association of druggists will hold its midwinter convention in Worcester. A portion of that afternoon will be given over to the Massachusetts Medical Society. Dr. Roger I. Lee, Dr. James C. McCann and the chairman of the Committee on Legislation have accepted invitations to speak during that period. The pharmaceutical profession of Massachusetts is bitterly opposed to the passage of the Wagner-Murray-Dingell Bill. As individuals, the druggists are doing more for the

doctor than the latter is doing for himself. Collectively, through committees, both professions are equally active.

The Committee on Legislation has given careful study to the part of the Wagner-Murray-Dingell Bill that pertains to the practice of medicine. We are convinced that passage of this legislation would bring about a regimentation of the American people into a federal system of socialized medicine and compulsory governmental hospitalization and bring about a dangerous revolution, which would be detrimental to health care. Plans are under way for a state-wide campaign in opposition to this pending legislation. The progress of this menacing threat to proper medical care for the American people is being watched each day by the members of this committee.

The committee believes, from conversations with many members of the Society, that it would be of advantage in many ways if a section of the *New England Journal of Medicine* could be devoted to medical economics. Such a section would, we believe, be welcomed by a majority. Most economic changes have or will come through legislation. Therefore this committee makes the suggestion.

Dr. Felton moved the acceptance of this report. This motion was seconded by a councilor.

Dr. Hyman Morrison, Norfolk, said that he thought the apparently unanimous opinion on the Wagner-Murray-Dingell Bill cannot be a true expression of what people are really thinking about it. He added: "Can it be such a terrible proposition that the unanimous opinion of the medical profession is against it. It is very gratifying to read the statement of the Massachusetts Medical Society in co-operation with the other state medical societies of New England."

Dr. Lee ruled that the Wagner-Murray-Dingell Bill was not under discussion at that time and that opportunity would be had for such discussion later in the meeting.

The report of the Committee on Legislation was accepted by vote of the Council.

Dr. Felton moved that the Committee on Legislation meet with the Committee on Publications to the end of devising methods of education in medical economics. This motion was seconded, and it was so ordered by vote of the Council.

Committee Appointed to Consult With Representatives of the other New England State Medical Societies Regarding the Wagner-Murray-Dingell Bills — Dr. Walter G. Phippen, Essex South, chairman.

This report (Appendix No. 7) was offered by Dr. Phippen. He referred the councilors to pages 1, 2 and 3 of the advance sheets of information for the full text of the report.

Dr. Phippen moved the acceptance of the report. This motion was seconded by a councilor and it was so ordered by vote of the Council.

Dr. Phippen moved that the Council approve the action of the Executive Committee in approving this report and authorizing the release of the following letter:

MASSACHUSETTS MEDICAL SOCIETY
6 Fenway, Boston

December 2, 1943

Dear Sir:

The Massachusetts Medical Society, in conjunction with the medical societies of Maine, New Hampshire, Vermont, Rhode Island and Connecticut, has studied Senate Bill 1161 and House Bill 2861 now before the

Congress of the United States and respectfully submits its views on this proposed legislation.

We approve of the broad medical objective of the act that we interpret to be an attempt to improve the health of the people. As a basis of our approval we cite the progressive leadership which the physicians of New England have always shown in the development of public-health enterprises. For more than fifty years we have consistently supported the plea for the establishment of a National Department of Health with a secretary in the President's Cabinet, under whom would be co-ordinated many important public-health programs, exclusive of the Army and Navy. These are now scattered through various departments and bureaus of the federal government and already play a large role in the provision of medical care for the people of this country.

We approve of the use of the insurance principle on a voluntary basis as a means to aid the individual to budget against the cost of medical care. We maintain that when insurance programs are not directly under the supervision of the medical profession by whom medical care is to be rendered, they should provide for cash benefits to be paid to the individual; for we firmly believe that the citizens of New England are capable of using cash benefits to pay the costs of medical care.

We believe that S. B. 1161 and H. B. 2861 do not provide for the sound development of a national health program. It is implied by the act that the distribution of compulsory savings managed by federal authorities will guarantee better health for all the people. We sincerely doubt that such objective can be realized in this way. In the New England states, judged by any standards with which we are familiar, there is no need to revolutionize the habits of the people in their methods of obtaining medical care.

Private enterprises in the field of voluntary prepaid medical and hospital insurance are increasing rapidly. *These facilities should be utilized by the states, if necessary through federal grants-in-aid, so that each state can purchase medical care for those who cannot purchase it for themselves.* This we believe to be a development that would be acceptable to the New England people, for thereby medical care could be provided even for the indigent who are public charges, a provision most desirable in those communities that have been unable or unwilling to meet this obvious responsibility.

We shall be glad to work out plans with representatives of the federal and state governments to improve the health of all the people, but we should expect that any plans that might be devised would take full advantage of existing agencies and be developed with the social patterns that are well understood by our people.

Very truly yours,

[Signed] Roger I. Lee
ROGER I. LEE, M.D., *President*
[Signed] Michael A. Tighe
MICHAEL A. TIGHE, M.D., *Secretary*

This motion was seconded by a councilor.

Dr. Hyman Morrison was recognized by the chair. He spoke as follows:

I want to apologize again that, in my zeal to bring up the discussion on the Wagner-Murray-Dingell Bill, I ran ahead of the program.

But it seems to me, I repeat, that a measure of such importance surely cannot but meet two points of view. As intelligent men we cannot accept a measure of such wide implication without giving it great thought and without feeling that there are two sides to the question. Few have read the bill: it covers over sixty pages. I admit I have not read it, but I did hear Senator Murray speak on it. If we have not thought about it or heard what the bill means to do, then unanimous acceptance or disapproval of it does no credit to any body of men.

It is gratifying that the medical societies of the New England states have met with great self-restraint the proposition now pending before Congress. A great stride forward has been taken when organized medicine began to approve voluntary medical insurance. That in itself indicates great progress in the thinking of our profession. It is not so long ago that any effort at prepayment medical service was considered taboo, and I think Dr. McCann will support me in this with his experience in the organization of the Massachusetts Medical Service. If nothing else, the health measures before Congress during the past decade have surely challenged the medical profession and have stimulated us to plan more adequate service for the low-income groups of the population.

The great objective of the bill is to give adequate medical care to the millions of people in America who do not get it. This may not apply to Massachusetts or Vermont, but nevertheless there are millions of people who cannot obtain good medical service without pauperizing themselves, as they do in the free clinics. This goes against the grain of human dignity. What the legislation under discussion proposes, in a broad way, is to make it possible for people with low incomes to get adequate medical care without pauperizing themselves — through compulsory insurance. This seems to me a great advance. It does not intend to do away with private practice; nor should it disturb the traditional cordial relation between physician and patient.

Why should it be different to the physician, worthy of the name, whether he is paid by the individual or through a collective fund?

It has been said that this sort of legislation is an infringement on our freedom as individuals. Now it seems to me that we take an attitude toward our government as if it were something foreign, coming in from the outside and infringing on our rights. Do we forget that the Government is what we make it? Our Congressmen are elected. The Government is the American people, responding to the will of the majority.

So I appeal, not particularly for this measure, but for a dignified attitude toward this type of legislation, and I am grateful as an individual to the officers of the New England medical societies for the broad aspect they have taken toward the bill.

It was suggested by Dr. J. Harper Blaisdell, Middlesex East, that when the vote on this question was taken it be by a show of hands. This suggestion met with the approval of the Council.

Dr. Schadt asked how it was that this letter was adopted before being submitted to the Council. Dr. Lee replied that it was published under authorization of the Executive Committee of the Council.

In response to the same question and on the invitation of the chair, Dr. Phippen spoke as follows:

We had several meetings and conferences with the members of the other state societies. They were very good to come and spend long afternoons with us in the Boston Medical Library. We usually spent three hours at a session, and we discussed almost every aspect of the Wagner-Murray-Dingell Bills. Dr. Morrison says he has not read the bill, and I venture to say that if we took a poll of this group here we should find that few of you have read the bill completely, and I cannot say that I blame you very much. It is very tiring and wearisome reading.

You asked us to study the bill and make some statement that would cover the consensus of a majority of the medical men. Now we do not say that these words that we have set down in print are the words that each one of you would have chosen if you were doing the same job that we had to do; but we believe, by and large, that they fairly represent the general opinion of medical men all over New England. At the second session we agreed to go our ways for a spell and to talk with all our neighbors and friends in order to ascertain how they felt about the bill. When we met again this letter was the result of the consensus. The other societies were anxious to get this into the hands of all the senators and representatives as soon as possible; and, since a meeting of the Council was not scheduled until today, we asked the Executive Committee if they would authorize us to go ahead and join with these other societies in releasing this statement, which the Executive Committee did.

The motion to approve the action of the Executive Committee of the Council was adopted, the vote being 176 for and 3 against.

Committee on Cancer — Dr. Ernest L. Hunt, Worcester, chairman.

Dr. Hunt announced that the full text of the report (Appendix No. 8) had appeared in the advance sheets of information beginning on page 9. He said that the report concerned itself with certain new regulations that had been set up by the Massachusetts Department of Public Health for the regulation of the state-aided cancer clinics. He added that the Committee on Cancer was not in accord regarding its recommendations anent these new regulations and that, therefore, a majority and a minority report

were submitted. He noted the absence of Dr Daland's name from the majority report. He explained that, although Dr Daland was not present at the last meeting of the committee, he did vote with the majority at an earlier meeting.

He added that the majority of the committee recommended that the Council take no action on these recommendations pending a six months' trial and that the minority recommended that the new regulations be not approved by the Council in so far as they relate to the collection of fees to be applied to the expense of conducting the clinics.

Dr John M. Fallon, Worcester, moved the acceptance of the report. This motion was seconded by a counselor, and it was so ordered by vote of the Council.

Dr Lee explained that Dr Hunt, not being a member of the Council, could not participate in the debate on this subject without the unanimous consent of the Council.

Dr David Cheever, Suffolk, moved that this consent be given. This motion was seconded by a counselor, and it was so ordered by vote of the Council.

Dr Frederick S. Hopkins, Hampden, moved the adoption of the majority report. This motion was seconded by a counselor.

Dr Felton asked the chair if this meant that one could ignore for six months anything that the Department of Public Health had to say regarding this. Dr Lee replied that he thought it meant that there would be no action by the Council during that time.

Dr Philemon E. Truesdale, Bristol South, said that he was one of those who voted in the committee to recommend deferment of action by the Council for six months. He added that the ruling put out by the Attorney General was, after all, the opinion of one lawyer and that, until its correctness was established by the courts, it could not be said to be constitutional. He referred to the survey of the state-aided cancer clinics recently made by Dr Channing Simmons and to its conclusion that sixteen clinics were doing excellent work and that in seven this work was substandard. He also spoke in a complimentary manner of the Fall River Clinic, under the chairmanship of Dr Thomas Almy, and said that these clinics are doing a work of charity for the common good. He thought that it might be wise to refer this matter to the attorneys of the Society for their interpretation.

Dr Charles C. Lund, Suffolk, in favoring the adoption of the majority report, said that the Department of Public Health was bound to follow the Attorney General's recommendation and that, as a consequence, this department had to set up certain new regulations. He added that the state-aided cancer clinics had been operating under these new regulations for two months. He spoke of a conversation that he had with Dr Lombard, during

the course of which he had been informed that, for this two-month period, a total of about \$69 had been collected under these new regulations and that this represented a little over \$2 per clinic per month.

Dr Bernard Appel, Essex South, in speaking in opposition to the adoption of the majority report, said that he was the dermatological consultant to the Lynn Cancer Clinic and that he looked up some figures which showed that between 50 and 60 per cent of the cases that are seen at this particular clinic are skin cases. He spoke of a woman who saw him at a skin clinic for 50 cents, she was then referred to the cancer clinic and saw him there for \$10. His conclusion was that there was something wrong with such a situation. "We say," he continued, "Let us charge them \$10 because that is the law, but we do not expect anybody to pay it—in other words, do not pay any attention to it."

Dr Phippen spoke as follows:

This cancer business seems to be quite a question and I think the fact is that the Attorney General has rendered a definite report that the Commissioner of Health is bound to follow, but for us today to accept the minority report and thereby upset the machinery that the Commissioner of Health has set up seems very unwise. The \$10 fee in the cancer clinic is ridiculous and something has got to be done about it. There is not much sense in charging such a fee and then saying to the patient, "Well you don't have to pay \$10. You can pay 50 cents and it will be all right." But I think we should accept the majority report with the understanding that the Committee on Cancer get busy with the Commissioner of Health to straighten the thing out. I am sure it is quite possible for him to come to some definite arrangement that is agreeable to the committee and to the Council. I am in favor of allowing them six months of grace to get busy and do something about it.

Dr Fallon said that he might have oversimplified this matter in his own mind, but that it looked to him as if the question was whether or not a person able to pay \$10 belonged in a state clinic.

Dr George A. Moore, Plymouth, emphasized the fact that the cancer clinics are diagnostic and that he would like very much to have these new regulations tried out for six months.

Dr Hunt was then invited by Dr Lee to enter the discussion. He spoke as follows:

I am sure that the diffused opinions we have just listened to show that there is some need of light in this picture—making statements that seem to be much beside the point of the matter. I might refer to Dr Lund's contention that it is too small to take any notice of by reminding you of the mother who thought that her unmarried daughter's illegitimate baby ought to be overlooked because it was so small. If I should use the cancer nomenclature I would say that this is just a little pimple. Compared with the Wagner Bill it is quite tiny—but it is just as important in its principle.

As chairman of the Committee on Cancer I venture to present a minority report at variance with that of the majority because of my conviction supported by the opinion of the Worcester Cancer Clinic Committee of which I am also chairman that the implications of certain features of the new rules and regulations are such as may embarrass those members of the Society who staff the clinics in the esteem of their fellows. Consequently the enlightened opinion of the Council is sought for their guidance and for its influence on the policies of the State Department of Public Health.

In other words, it is a matter involving the question whether it is right or wrong, whether it is ethical and proper or not. But the thing they have not mentioned is that, whereas a fee of \$10 is the upper limit, they do not exclude anybody. Any millionaire can walk in and get that service for \$10, and that is where it reflects against the medical profession.

The objectionable features are found in those clauses which relate to the collection of fees for clinic services and the use of the funds realized from such fees.

It is contended that the plan (1) extends state medicine beyond the intent of the Constitution, (2) exploits the voluntary services of the clinic staffs to reduce the cost of the clinics to the State, (3) puts the clinics into unfair competition with private consultants, including their own staff members and (4) puts an unfair burden of legal responsibility on the unpaid members of this society who head the local clinics. Let us examine these contentions in more detail:

(1) *The new plan extends state medicine beyond the intent of the Constitution.* So long as a state agency offers to sell, under whatever guise, medical services to persons outside the indigent and near indigent classes, at rates equivalent to those accepted by local custom for private sources of the same services, it is invading the field of free medical enterprise. It thereby violates the spirit of the constitution and good public policy. It cannot, in fairness, require practitioners of medicine to comply with its own educational and quality of service standards through license to practice and then undermine their field in order to ease its own financial commitments whenever it decrees it expedient to do so.

Heretofore the clinics have been a co-operative effort between the Department of Public Health, the physicians and the hospitals. Because of the universality of the cancer problem and the supposed taxpayers' rights no limitation has been placed on who should be received for consultation and diagnosis in the clinics. Since no fees were charged and no financial gain accrued to either member of the co-operative group, no one found fault until the Attorney General discovered that, in serving persons able to pay, the Department of Public Health, through the clinics, was violating the Constitution. So the Department devised this new plan, and in order to "as far as possible maintain the former status of the clinics" (quoted from letter of Dr. Getting of January 21, 1944) put them on a pay basis for persons above the indigent level and fixed a fee of \$10 or fraction thereof. Such a fee is equivalent to private consultation fees in many parts of the state.

(2) *Exploits the voluntary services of the clinic staffs to reduce the cost of the clinic to the State.* The rules provide that even though fees of \$10 are to be charged those patients able to pay, the services of hospital and medical staff remain on a gratuitous, contributory basis.

Who gets the money? At the end of the month all receipts from fees are deducted from the bill sent the State for the expenses of the clinic; therefore, the state gets it. Thus medical charity is extended beyond the needy patient to the treasury of the Commonwealth. The remedy is to give up the pay clinics or to pay doctors and hospitals.

(3) *Puts the clinics into unfair competition with private consultants.* The rules provide no authority whereby any citizen, however opulent, may be excluded from the benefits of the clinics. On the other hand, they offer him a bargain for they require the presence of a surgeon, a pathologist and a radiologist at each clinic so that the patient shall have the benefit of so-called "group diagnosis." When the average purchaser can get the services of three clinic experts for the price of one private expert, which will he be likely to choose?

A feeble attempt to prevent this exploitation is found in the foreword to the rules and regulations, wherein the referring doctor is permitted to provide the clinic with information in regard to the patient's ability to pay, but whether he does or not the clinic has no authority to exclude the patient and is obligated to collect fees from him if the doctor says he is able to pay.

The referral card that doctors are supposed to use, but seldom do, suggests to the doctor that he decide what persons are eligible to clinic services but does not make the patient's admission conditional on his doing so. If he does give any information the clinic must take his word for it.

(4) *Puts an unfair burden of legal responsibility on the unpaid members of this society who head the local clinics.* To save time I think I shall not press this point now.

I just took this attitude on the majority report because I thought that this whole subject should be brought out into the light of day, so to speak. Please be assured that I do not wish to break down the clinics; I desire to put them on a sound basis of service to the indigent or near indigent. I have been with the state cancer program from the beginning — now seventeen years. I want to continue but I also want to do so in good conscience.

I want to say, in conclusion, that we cannot govern the State Department of Public Health, and it is to promote the discussion of this problem that I am asking your opinion today.

Dr. Bagnall spoke as follows:

As a matter of attitude as a member of the Council, my feeling is that we should go 51 per cent of the way in co-operation with the Department of Public Health. As a member of the Public Health Council I feel that I want to go at least 51 per cent of the way in co-operation with the Massachusetts Medical Society, and I know that that is the attitude of the Public Health Council, as well as of the Commissioner.

If you remember the phraseology of this law, it states that the Department of Public Health shall operate a clinic for cancer with or without the co-operation of organized medicine. So far as the legal angles are concerned, I think the suggestion of Dr. Truesdale is an excellent one. It is difficult for a body of this sort to get down to the important fundamental factors that would put us in position to decide what we ought to do. It must be apparent to all of you that that is necessary. That is why I should leave it to the members of the committee.

I have not heard Dr. Hunt say anything about a memorandum that the Commissioner published; but Dr. Lombard, at my request, produced it. It is to the effect that when patients are referred to the clinics by the attending physicians, the latter shall have a chance to follow the medically indigent. The clinics are instructed by the Commissioner and Dr. Lombard to inquire about the medical indigency of those patients who come in, who filter in through the family physician, and to direct that those people go to a private physician. That seems to be an answer to the statement that the state is practicing medicine on those who are not medically indigent.

In the matter of fee, Dr. Hunt, I think, contends only for two things. One is that we be not put in competition with ourselves so far as taking people who are not medically indigent is concerned. I think the Department of Public Health and the Committee on Cancer have definitely taken that stand and are in agreement. The only thing that remains then, is whether we have a \$2 fee, as Dr. Hunt asks, or a \$10 fee.

The \$10 fee does not cover the cost. The cost of any patient on the average is more than \$20, as all the facts show on the basis of medical indigency. I am very sure that, if \$10 is too high a fee, there can be an adjustment between the Department of Public Health and the Massachusetts Medical Society. Someone said that the intent of the law was that every patient should pay \$10. I think that is a mistake. The \$10 was stated as the fee, with gradations downward according to the degree of medical indigency.

There is another matter that perhaps you have not in mind but that I have in mind. I may be anticipating this. I have given it considerable thought and have not come to any fixed opinion. It has been stated that the Department of Public Health is presuming to direct the procedure that is offered in the State. The Department of Public Health would not have any right under those plans to reduce the fee of any patient by a dollar, even if he were not medically indigent.

With these general principles, we should be rather careful about taking any position hostile to the Department of Public Health. Perhaps I am not the man to say that but I do think that we can get along better with the department, and they with us, if we give and take and not throw brickbats.

Dr. Richard M. Smith assured the Council that the attitude of the Commissioner is not to attempt

any arbitrary procedure. He added that the plan proposed was the least objectionable of three possibilities. Finally, he expressed the hope that the Council would not take any decisive action.

Dr. William Dameshek, Norfolk, said that it seemed paradoxical to disapprove so overwhelmingly a medical program that had to do with socialized medicine and then to allow a plan of which the profession as a whole is ignorant. He mentioned that the Attorney General might allow the department, on the basis of this ruling, to put in clinics with reference to anemia or thyroid or renal conditions. He expressed as his final thought that this matter deserved further study on the part of the committee and Council.

Dr. Schadt said that, if this proposition were accepted, the Council might just as well accept the Wagner-Murray-Dingell Bill. He added, however, that he favored the majority report.

Dr. Hunt referred to the memorandum that Dr. Bagnall had previously mentioned. In reading it, he asked the councilors to listen carefully and see if they could make out what it meant:

Whereas, 85 per cent of the patients coming to the cancer clinics are referred by the family physician who knows whether these patients are able to afford full diagnostic service, the department recommends that of the 15 per cent of the patients applying directly to the clinic for diagnosis, those who upon investigation are found not to be in whole or in part unable to pay for their own diagnosis be referred to a private physician.

Dr. Hunt referred to Dr. Bagnall's statement that it costs \$20 per patient. He then read from the regulations as follows:

In this way the State pays for none of the services to individuals who can pay for themselves and only for a part of the services of "such persons as may be in whole or in part unable to support or care for themselves," as both physicians and hospitals contribute materially to all groups.

If it costs \$20 to see a patient, he continued, and the charge is only \$10, he did not see how the word "none" came in at all.

Finally, Dr. Hunt said that he had been in this work ever since it started and that he would be glad to continue but that he could not with a clear conscience continue to do so under these rules.

Dr. Leroy E. Parkins, Suffolk, moved as an amendment that the words "until the May meeting" be substituted for the words "for at least six months." This amendment was seconded by a councilor. It was adopted by vote of the Council.

The chair announced that the motion as amended read as follows:

It [the majority] recommends, however, that any action on these regulations by the Council of the Massachusetts Medical Society be postponed until the May meeting, so as to observe the manner in which the clinics function under these new regulations.

The motion as amended was put and was adopted by vote of the Council.

War Participation Committee—Dr. William B. Breed, Suffolk, chairman.

The report (Appendix No. 9) was offered by Dr. Breed. Dr. Breed moved that the report be accepted as a report of progress. This motion was seconded by a councilor, and it was so ordered by vote of the Council.

Committee on Rehabilitation—Dr. William E. Browne, Suffolk, chairman.
No report.

Postwar Loan-Fund Committee—Dr. George Leonard Schadt, Hampden, chairman.

The report (Appendix No. 10) was presented by Dr. Schadt, who moved its acceptance as one of progress. This motion was seconded by a councilor and it was so ordered by vote of the Council.

Military Postgraduate Committee—Dr. W. Richard Ohler, Norfolk, chairman.

The report (Appendix No. 11) was offered by Dr. Ohler, who moved its acceptance. This motion was seconded by a councilor, and it was so ordered by vote of the Council.

Committee to Aid the District Rationing Administrator—Dr. Joseph Garland, Suffolk, chairman.
Dr. Garland reported as follows:

Since its last report to the Council, this committee has met each month with the district rationing officer, aiding in various problems associated with the medical aspects of food rationing. In addition, the members of the committee have individually considered a number of doctors' certificates of patients' necessity. The excellent recommendations of the Subcommittee on Medical Food Requirements of the National Research Council, as published in the October 16 and 23, 1943, issue of the *Journal of the American Medical Association*, have been carefully studied, and have been adopted with liberal interpretations, so far as they have seemed to apply to local conditions.

A comprehensive report on the activities of the committee and the policies it has followed was published in the January 13, 1944, issue of the *New England Journal of Medicine*.

A problem was encountered in the request of the Moore Drop Forging Company, of Springfield, for extra meat allowances for several hundred of its employees who were working long hours at the open forge and in the heat treatment of metal. The request was made on the basis of undue fatigue and extreme loss of weight. It is interesting that no similar request, so far as can be ascertained, has been made by other plants of this type, here or elsewhere. As the decision in this case might be used widely as a precedent, however, advice was sought from the Harvard Fatigue Laboratory and the State Department of Public Health, and a hearing was held on January 5, 1944, at which your committee, officers of the regional and national OPA, and representatives of the Department of Public Health, the Massachusetts Department of Labor and Industry and the Harvard Fatigue Laboratory met with a medical representative of the Moore Drop Forging Company. No action favoring the request was taken, and the services of Dr. Robert S. Goodhart, chief of the Industrial Feeding Programs Division of the War Food Administration, have been enlisted to visit the plant and survey existing conditions.

FRANKLIN W. WHITE
F. GORHAM BRIGHAM
JOSEPH GARLAND, Chairman

Dr. Garland moved the acceptance of the report as one of progress. This motion was seconded by a councilor, and it was so ordered by vote of the Council.

Committee to Look into the Possibility of Better Publicity for the Massachusetts Medical Society — Dr. Albert A. Hornor, Suffolk, chairman.

No report.

Committee to Meet With the Trustees of Middlesex University — Dr. Reginald Fitz, Suffolk, chairman.

No report.

Committee on Postgraduate Instruction — Dr. Fitz, chairman.

No report.

Committee on Physical Therapy — Dr. Arthur L. Watkins, Middlesex South, chairman.

Dr. Watkins reported as follows:

In view of the value of physical therapy as an aid in the physical rehabilitation of industrial and war casualties, this committee has actively co-operated with the New England Committee for Wartime Graduate Medical Meetings in arranging monthly symposiums on physical therapy. Education of civilian and military physicians concerning the indications for physical therapy and the procedures to be prescribed appears especially important at this time. Future developments will be dependent on the role of civilian medicine in caring for the discharged service men. The Committee on Physical Therapy and the Rehabilitation Committee are working together and will be ready to provide advice and aid in whatever program is accepted by the Massachusetts Medical Society and the federal government.

Dr. Watkins moved the acceptance of this report as one of progress. This motion was seconded by a councilor, and it was so ordered by vote of the Council.

Committee to Consider Expert Testimony — Dr. Frank R. Ober, Suffolk, chairman.

No report.

Committee on Automobile Insurance Claims — Dr. Henry C. Marble, Suffolk, chairman.

No report.

Committee on Convalescent Care — Dr. T. Duckett Jones, Suffolk, chairman.

The Secretary announced that Dr. Jones had requested the discontinuance of this committee. The Secretary moved its discontinuance. This motion was seconded by a councilor, and it was so ordered by vote of the Council.

Committee to Study the Practice of Medicine by Unregistered Persons — Dr. Richard Dutton, Middlesex East, chairman.

No report.

Committee to Meet with the Massachusetts Hospital Association — Dr. Walter G. Phippen, Essex South, chairman.

No report.

Committee on Maternal Welfare — Dr. Judson A. Smith, Suffolk, chairman.

No response.

Committee on Ways and Means to Conserve Physicians' Energies — Dr. Elmer S. Bagnall, chairman.

No report.

APPOINTMENTS

President Lee made the following appointments of Delegates to the House of Delegates, American Medical Association, for two years beginning June 1, 1944:

<i>Delegates</i>	<i>Alternates</i>
David D. Scannell, Jamaica Plain	Elmer S. Bagnall, Groveland
Dwight O'Hara, Waltham	Ernest L. Hunt, Worcester
Charles E. Mongan, Somerville	Charles J. Kickham, Brookline
Walter G. Phippen, Salem	John I. B. Vail, Hyannis

Dr. William M. Collins, Middlesex North, moved that these appointments be confirmed. This motion was seconded by a councilor, and it was so ordered by vote of the Council.

Dr. Lee designated the following delegates to the annual meetings of the medical societies of the other New England states:

Maine: Warren H. Sherman, Lowell, and Frank W. Snow, Newburyport
New Hampshire: Peirce H. Leavitt, Brockton, and Daniel J. Ellison, Lowell
Vermont: George D. Henderson, Holyoke, and George L. Steele, Springfield
Rhode Island: George A. Buckley, Brockton, and Charles D. McCann, Brockton
Connecticut: Clarence E. Burt, New Bedford, and Edward P. Bagg, Holyoke

It was moved and seconded that these nominations be approved. It was so ordered by vote of the Council.

Dr. Lee appointed Dr. Reginald Fitz as delegate to the Annual Congress on Medical Education and Licensure, American Medical Association. It was moved and seconded that this appointment be confirmed. It was so ordered by vote of the Council.

Dr. Lee made the following *ad interim* appointments:

Committee to Look into the Possibility of Better Publicity for the Massachusetts Medical Society: Albert A. Hornor, chairman; Michael A. Tighe, Robert N. Nye, Norman A. Welch, Walter H. Pulsifer.
Committee to Meet with the Trustees of Middlesex University: Reginald Fitz, chairman; Robert T. Monroe, Daniel B. Reardon, Donald Munro, Harold L. Musgrave, Dr. William E. Browne, representing Suffolk, to the Committee on Legislation.

It was moved and seconded that these appointments be approved. It was so ordered by vote of the Council.

NEW BUSINESS

Dr. Jacob Fine, Suffolk, was recognized by the chair. Dr. Fine spoke as follows:

The Council may be interested in certain data regarding the foreign physicians licensed in Massachusetts. According to the *American Medical Directory* and the files of the

Boston Committee on Medical Emigres a total of 163 foreign physicians were licensed to practice in this state since 1934. The Committee on Medical Emigres has data in its files on all but 35 of the total number — that is it knows the type of activity and the location of settlement of 130 of them. They are distributed as follows: 40 hold institutional positions exclusively, 66 practice a specialty or are in general practice in large or medium-sized cities, and 23 practice in small towns. They are settled in all parts of the State. Of the total number, 72 are members of the Society and 92 have not been admitted.

With these facts in mind the following questions present themselves:

(1) Have any of the 72 foreign physicians who are members of the Society and who became members before the amendment to the by-laws was adopted acted unethically? Have any of them acted so as to prejudice the interests of the Society, their fellow practitioners or the profession at large?

(2) Of the 92 foreign physicians who are not members of the Society, all but 5 have been licensed for two or more years. Twenty-four hold institutional positions, 68 are in various specialties and general practice. Of this group of 68, have any acted during these two or more years in such a way as to prejudice the interests of their fellow practitioners or the profession at large?

The Committee on Medical Emigres has received complaints in three instances, in one case it could not get sufficient information, in a second, in which the physician was undesirably publicized in a newspaper shortly after his settlement, there was evidence that the physician was taken in by an overzealous young lady reporter apparently anxious to get material, and in the third case now under investigation, the evidence is incomplete and conflicting, but the weight of evidence from the community itself is overwhelmingly in the physician's favor.

Rumors, vague accusations and generalizations regarding the demerits of these foreign physicians have been numerous, but specific demonstrable incidents of unacceptable practices have been exceedingly scarce and not out of proportion to what we experience among native born physicians.

At the annual meeting in May, 1942, 44 per cent of those voting on the amendment to the by-law disapproved it. The Committee on Medical Education unanimously disapproved it. The machinery for excluding undesirable physicians from the Society existed before the amendment was adopted.

What experience does the Society or the profession have before or since the adoption of the amendment that justifies its continuance in its present form? The threat of inundation of the State by foreign physicians was never real, and today there is only a rare individual who might settle here even if he were encouraged to do so.

It therefore seems appropriate for the Council to consider whether or not the amendment to the by-law is unnecessarily restrictive in its five year exclusion provision.

Dr Fine moved that the Committee on Membership be instructed to reinvestigate the merits of the five-year exclusion provision of the recent amendment with a view to reducing the time after a license is granted before membership in the Society is permissible. This motion was seconded by a councilor, and it was so ordered by vote of the Council.

Dr Phippen said that, when he was president of the Society, he had expressed the hope that when sufficient space was available an information bureau at the headquarters might be established. He added that there was now plenty of space. He moved that the President appoint a committee, which would include the Secretary, to study the question of establishing a bureau of information and its proper location in the Boston Medical Library. This motion was seconded by a councilor, and it was so ordered by vote of the Council.

There being no other business, the Council adjourned at 1:50 p.m.

MICHAEL A TIGHE, Secretary

APPENDIX NO 1

ATTENDANCE

BARNSTABLE	Richard Dutton
C H Keene	E M Halligan
J G Kelley	R W Layton
W D Kinney	R R Stratton
	J M Wilcox
BERKSHIRE	MIDDLESEX NORTH
I S F Dodd	H R Coburn
C F Kernan	W M Collins
Solomon Schwager	A R Gardner
P J Sullivan	H M Larrabee
BRISTOL NORTH	W F Ryan
W H Allen	W H Sherman
J H Brewster	M A Tighe
R M Chambers	MIDDLESEX SOUTH
W J Morse Jr	C F Atwood
W M Stobbs	E W Barron
BRISTOL SOUTH	J D Bennett
G W Blood	G F H Bowers
F D Gardner	Madeleine R Brown
C C Tripp	R W Buck
P E Truesdale	J F Casey
Henry Wardle	H F Day
ESSEX NORTH	C L Derick
F S Bagnall	Emilio D'Yrrio
R V Baketel	C W Downing
J T Batat	J G Finnerty
L R Chaput	H G Giddings
N I DeCesare	H W Godfrey
E H Ganley	J L Golden
P J Iook	A D Guthrie
G I Richardson	Elhot Hubbard, Jr
F W Snow	A M Jackson
C F Warren	F R Jouett
ESSEX SOUTH	F E Kattwinkel
Bernard Appel	A A Levi
H A Boyle	A N Makechnie
C L Curtis	Dudley Merrill
Joring Grimes	J P Nelligan
P P Johnson	E J O'Brien Jr
A T Parkhurst	Dwight O'Hara
W G Phippen	Fabyan Packard
E D Reynolds	S H Remick
H D Stebbins	L H Robbins
P E Tivnan	M J Schlesinger
J W Trask	H W Thayer
C T Twomey	A B Toppin
C A Worthen	J E Vance
FRANKLIN	Fresenius Van Nuy
A W Hayes	C F Walcott
H M Kemp	Hovhannes Zovickian
HAMPDEN	NORFOLK
F H Allen	Carl Beare
F P Bagg	Arthur Berk
W A R Chapin	M I Berman
J I Chereskin	G F Blood
P E Gear	J H Carey
Frederic Hagler	D J Collins
G D Henderson	William Dameshek
F S Hopkins	G L Doherty
Charles Jurist	Albert Ehrenfried
M W Pearson	H M Emmons
A G Rice	J C V Fisher
G L Schadt	Susannah Friedman
MIDDLESEX EAST	J B Hall
J H Blaisdell	H B Harris
R M Burgoyne	R J Heffernan
C W De Wolf	H J Inglis
	P J Jakmauh
	I R Jankelson

- C. J. Kickham
C. J. E. Kickham
E. L. Kickham
H. M. Landesman
D. S. Luce
C. M. Lydon
D. L. Lynch
F. P. McCarthy
H. L. McCarthy
R. T. Monroe
Hyman Morrison
D. J. Mullane
M. W. O'Connell
G. W. Papan
S. A. Robins
Kathleyne S. Snow
J. W. Spellman
J. P. Treanor, Jr.
W. J. Walton
N. A. Welch

NORFOLK SOUTH
C. S. Adams
D. L. Belding
R. L. Cook
N. R. Pillsbury
D. B. Reardon
H. A. Robinson

PLYMOUTH
G. A. Buckley
P. B. Kelly
P. H. Leavitt
C. D. McCann
J. J. McNamara
G. A. Moore
W. H. Pulsifer

SUFFOLK
A. W. Allen
W. B. Breed
W. J. Brickley
W. E. Browne
G. C. Caner
David Cheever
Pasquale Costanza
G. B. Fenwick
Jacob Fine
Reginald Fitz
Maurice Fremont-Smith
Joseph Garland
F. C. Hall
A. A. Horner

L. M. Hurxthal
C. S. Keefer
R. I. Lee
C. C. Lund
W. J. Mixer
Donald Munro
H. F. Newton
R. N. Nye
F. R. Ober
F. W. O'Brien
J. P. O'Hare
L. E. Parkins
L. E. Phaneuf
Helen S. Pittman
W. H. Robey
H. F. Root
R. M. Smith
M. C. Sosman
E. F. Timmins
J. J. Todd
Conrad Wesselhoeft
C. F. Wilinsky
- WORCESTER
C. R. Abbott
A. W. Atwood
George Ballantyne
Gordon Berry
W. P. Bowers
J. J. Dumphy
J. M. Fallon
L. M. Felton
E. R. Leib
L. P. Leland
W. F. Lynch
J. C. McCann
A. E. O'Connell
H. L. Paine
R. S. Perkins
C. A. Sparrow
O. H. Stansfield
R. J. Ward
R. P. Watkins

WORCESTER NORTH
E. A. Adams
H. D. Bone
C. B. Gay
G. P. Keaveny
F. A. Reynolds
J. G. Simmons
B. P. Sweeney

SCHEDULE A: Statement showing the balance sheet of The Massachusetts Medical Society, December 31, 1943.

SCHEDULE B: Statement showing the revenue and expenses of The Massachusetts Medical Society for the twelve months ended December 31, 1943.

The cash balance at December 31, 1943 was verified by direct correspondence and reconciliation. The cash receipts as recorded have been deposited in the bank, and disbursements are supported by vouchers or cancelled checks.

The securities and savings bank books were examined or accounted for.

The Building Fund and General Fund securities are listed in separate exhibits showing book and market values as of December 31, 1942 and December 31, 1943.

The market prices were furnished by Loomis-Sayles Inc. who also submit quarterly the average yield for both the Building and General Fund investments.

The profit or loss on securities sold, called or matured of the Building Fund and General Fund is shown under separate exhibits. The income from securities has been properly accounted for. During 1943, there has been no amortization of bond premiums.

The accompanying balance sheet and related statement of revenue and expenses fairly present the position of the Massachusetts Medical Society at December 31, 1943, and the results of operations for the year ended on that date.

Respectfully submitted,
HARTSHORN AND WALTER

50 Congress Street
Boston

* * *

SCHEDULE A		
STATEMENT SHOWING THE BALANCE SHEET OF THE MASSACHUSETTS MEDICAL SOCIETY, DECEMBER 31, 1943		
ASSETS		
Fund Securities and Cash		
Endowment Funds.....	\$23,166.87	
Building Fund.....	66,566.69	
General Fund.....	160,651.91	
Total.....		250,385.47
LIABILITIES AND FUND ACCOUNTS		
Fund Accounts		
Endowment Funds:		
Shattuck Fund:		
G. C. Shattuck 1854-1866.....	9,166.87	
Phillips Fund:		
Jonathan Phillips 1860.....	10,000.00	
Cotting Fund:		
B. E. Cotting \$1,000 — 1876-1881-1887.....	3,000.00	
Brickley Fund:		
William J. Brickley \$1,000 — 1943 ..	1,000.00	
		23,166.87
Building Fund.....		66,566.69
General Fund.....		160,651.91
Total.....		250,385.47

APPENDIX NO. 2

REPORT OF THE AUDITING COMMITTEE

The Auditing Committee appointed the firm of Hartshorn and Walter, accountants and auditors, to audit the books and accounts of the Massachusetts Medical Society.

The accountants have submitted to us an analysis of the revenues and expenses of the Society and a balance sheet of the condition of the Massachusetts Medical Society as of December 31, 1943.

We have examined their report and the various schedules submitted.

Fritz B. Talbot
Harry Linenthal

* * *

January 28, 1944

The Auditing Committee:
Fritz B. Talbot, M.D.
Harry Linenthal, M.D.

The Massachusetts Medical Society
8 The Fenway
Boston, Massachusetts

Gentlemen:

We have completed our examination of the books and accounts of The Massachusetts Medical Society for the twelve months ended December 31, 1943 and submit herewith:

SCHEDULE A EXHIBIT 1			
ENDOWMENT FUNDS, DECEMBER 31, 1943			
	Securities and Cash	Income	
Shattuck Fund			
Annuity Policy — Massachusetts Hospital Life Insurance Co. Certificate No. 438.....	9,166.87		183.34
Phillips Fund			
\$10,000 Commonwealth of Massachusetts 3½s Jan. 1, 1944 (Reg.).....	10,000.00		350.00
Cotting Fund			
Deposit — Institute for Savings in Roxbury, No. 45252.....	1,000.00		17.50
Deposit — Provident Institution for Savings in Boston, No. 1828.....	1,000.00		20.00
Deposit — Suffolk Savings Bank, No. 68364..	1,000.00		15.00
Brickley Fund			
Deposit — Warren Institution for Savings, No. 148845.....	1,000.00		13.33
Totals.....	23,166.87		599.17

SCHEDULE A EXHIBIT 2			
BUILDING FUND, DECEMBER 31, 1942 AND 1943			
		BOOK VALUE	
		December 31, 1942	December 31, 1943
Par or Shares	SECURITIES		
\$5,000	American Tel. & Tel. Co. 3s Sept. 1, 1956...		5,863.37
1,000	Blackstone Valley Gas & Electric Series C4s, Nov. 1, 1965.....	1,025.00	
1,000	Canada, Dominion of, 3s, Nov. 15, 1968...	972.50	972.50

1000	Central Pacific Ry Co 1st Ref Mtg 4s Aug 1960		71 ⁻ / ₈₀		2000	Great Northern Ry Co Gen Mtg B 3½s Jan 1 1952		1932 30	1931 50
1000	" "		977 78		1000	Great Northern Ry Co 1st & Ref 4½s July 1 1961		990 30	990 30
500	" "		400 00	400 00	1000	Great Northern Ry Co Gen Mtg Gold Series 13½s Jan 1 1967		975 00	975 00
1000	" "				4000	Great Northern Ry Co 4¼s Jan 1 1961		4483 02	
	" "		1 125 83		2000	Hiram Walker Gooderham & Worts Ltd 1s Nov 1 1943		2 000 00	
	" "			414 69	1000	Jacksonville Terminal Co Series B Ref & Fret Mtg Gold 6s July 1 1967		1 065 00	1 065 00
	" "		1 045 00		3000	Lorillard Co Deb 3s Apr 1963 Temp Without Coupons		3 033 75	
	" "		1 015 00	1 015 00	1000	" " " " " " " " " "		1 010 00	
	" "		1 030 00	1 030 00	1000	" " " " " " " " " "		1 005 00	1 005 00
	" "		1 010 00		2500	" " " " " " " " " "		2 563 33	
	" "		1 005 00	1 005 00	2000	" " " " " " " " " "		2 080 00	2 080 00
1000	Monongahela Ry Co 1st Mtg Series B 3½s Feb 1 1966		1 075 00	1 075 00	1000	Monongahela Ry Co 1st Mtg Series B 3½s Feb 1 1966		1 025 00	1 075 00
2000	N Y Central R R S F Sec 3½s Apr 1 1946		1 960 00		3000	Nat'l Sav & Loan Ass'n 3s Dec 1 1945		390 00	
1200	N Y Chicago & St Louis R R Notes 6s June 1 1950		1 200 00		2000	Nat'l Sav & Loan Ass'n 3s Dec 1 1945		2 000 00	2 000 00
1000	" " " " " " " " " "		801 75	801 25	1000	New Brunswick Prov of Deb 3½s July 1 1960		1 000 00	1 000 00
**	" " " " " " " " " "		1 010 00		2000	Nat'l Sav & Loan Ass'n 3s Dec 1 1945		2 040 00	2 040 00
**	" " " " " " " " " "		984 14	984 14	1000	Nat'l Sav & Loan Ass'n 3s Dec 1 1945		980 00	
.	" " " " " " " " " "		1 016 00	1 930 56	1000	" " " " " " " " " "		937 50	937 50
.	" " " " " " " " " "		1 930 56		600	" " " " " " " " " "		600 00	
**	" " " " " " " " " "		1 035 00	1 035 00	1000	Quebec Province of 3s July 1 1950		1 005 00	1 005 00
**	" " " " " " " " " "		1 037 90	1 037 90	1000	Remington Rand Inc S F Deb 3½s July 1 1956		995 37	995 37
1000	" " " " " " " " " "		700 00	700 00	3000	Remington Rand Inc S F Deb 3½s July 1 1956		3 112 50	
1000	" " " " " " " " " "		1 000 00		1000	Revere Copper & Brass Co 1st Mtg 3½s Jan 1 1960		1 075 00	
4000	" " " " " " " " " "		1 000 00		2000	" " " " " " " " " "		2 100 00	2 100 00
1000	" " " " " " " " " "		2 960 00	2 960 00	2000	" " " " " " " " " "		1 605 00	
8000	" " " " " " " " " "		3 000 00	8 000 00	1000	" " " " " " " " " "		1 025 00	1 025 00
2000	" " " " " " " " " "		7 045 00	2 015 00	1000	" " " " " " " " " "		1 037 97	1 037 97
1000	" " " " " " " " " "		1 030 00	1 030 00	2000	Texas Corp Deb 3s Apr 1, 1959		2 020 00	2 070 00
19000	" " " " " " " " " "		19 000 00	1 000 00	1000	Toledo Edison Co 1st Mtg 3½s July 1 1960		1 015 00	
	" " " " " " " " " "		1 130 00	2 067 20	5000	" " " " " " " " " "		5 031 64	
	" " " " " " " " " "			2 100 90	3000	" " " " " " " " " "		3 040 00	
	" " " " " " " " " "			15 74	3000	" " " " " " " " " "		3 000 00	3 000 00
	" " " " " " " " " "		383 40	387 24	5000	U S A Treasury 2½s 1943-43		5 225 00	
	" " " " " " " " " "		1 921 90	1 960 52	2000	U S A Treasury 2½s 1955-51 (Reg)		2 000 00	2 000 00
	Total Securities		(0 074 65	62 449 67	5000	U S A Treasury 2½s 1949-51		5 000 00	
Uninvested Cash				2 780 87	3000	U S A Treasury 2½s 1972-67 (Reg)		3 000 00	3 000 00
Mercantile National Bank			3 917 15	8 836 20	500	U S Treasury Note 4½s Dec 15 1945		500 00	500 00
New England Trust Co					2000	U S A Treasury ¾s Nov 2 1943		2 000 00	
Totals			63 991 90	66 566 67	35000	U S A Defense Savings 2½s 1955 G			35 000 00

SCHEDULE A EXHIBIT 3
GENERAL FUND DECEMBER 31 1942 AND 1943

Par or Shares	SECURITIES		Book Value	December	December
			31, 1942	31, 1943	31, 1943
\$10,000	American Tel & Tel Co 3s Sept 1 1956				11 071 74
2,000	Atlantic Coast Line R R Co 1st Cons		1 503 04		
"	"		3 142 50		
"	"		1 025 00		
"	"		1 015 00		1 015 00
"	"		1 070 00		
"	"		7 030 00		2 050 00
"	"		5 000 00		
"	"		2 155 70		
1,000	Connecticut River Power Co 1st Series A 3 1/2s Feb 15 1961		1 015 00		
2,000	Consumers Power Co 1st Mtg 3 3/4s Nov 1, 1969		2 110 00		
2,000	Conveyancers Title Insurance & Mtg Co 4 1/2s Dec 1 1937 (In Default) Written Down		400 00		
583 30	Conveyancers Realty Co 15 Yr Deb 4s 1957				107 54
1,000	"		1 015 00		
5,000	"		5 270 00		5 270 00
2,000	"		2 000 00		2 000 00
2,000	First Railroad Co 4s Jan 1 1935		2 000 00		2 000 00
1,000	Fort Street Un on Depot Co 1st Mtg 3 1/2s Dec 1 1963		1 000 00		1 000 00

2 000	Great Northern Ry Co Gen Mtg B 5½s Jan 1 1952	1 932 30	1 932 50
1 000	Great Northern Ry Co 1st & Ref 4½s July 1 1961	990 30	990 30
1 000	Great Northern Ry Co Gen Mtg Gold Series 1½s Jan 1 1967	975 00	975 00
4 000	Great Northern Ry Co 4½s Jan 1 1961		4 483 02
2 000	Hiram Walker Gooderham & Worts Ltd 1s Nov 1 1943	2 000 00	
1 000	Jacksonville Terminal Co Series B Ref & Fst Mtg Gold 6s July 1 1967	1 065 00	1 065 00
3 000	Lorillard Co Deb 3s Apr 1963 Temp Without Coupons		3 033 75
1 000	" " " " " " " " " "	1 010 00	
1 000	" " " " " " " " " "	1 005 00	1 005 00
2 500	" " " " " " " " " "	2 563 33	
2 000	" " " " " " " " " "	2 080 00	2 080 00
1 000	Monongahela Ry Co 1st Mtg Series B 3½s Feb 1 1966	1 025 00	1 075 00
3 000	N " " " " " " " " " "	350 00	
2 000	Ne " " " " " " " " " "	2 000 00	2 000 00
1 000	New Brunswick Prov of Deb 3½s July 1 1968	1 000 00	1 000 00
2 000	Ne " " " " " " " " " "	2 040 00	2 040 00
1 000	Ne " " " " " " " " " "	980 00	
1 000	" " " " " " " " " "	937 50	937 50
600	" " " " " " " " " "	600 00	
1 000	Quebec Province of 1s Jan 1 1970	1 005 00	1 005 00
1 000	Quebec Province of 1s Jan 1 1970	995 37	995 37
3 000	Remington Rand Inc S F Deb 3½s July 1 1956	3 112 50	
1 000	Revere Copper & Brass Co 1st Mtg 3½s	1 075 00	
2 000	" " " " " " " " " "	2 100 00	2 100 00
2 000	" " " " " " " " " "	1 605 00	
1 000	" " " " " " " " " "	1 025 00	1 075 00
1 000	" " " " " " " " " "	1 037 97	1 037 97
2 000	Texas Corp Deb 3s Apr 1, 1959	2 020 00	2 070 00
1 000	Toledo Edison Co 1st Mtg 3½s July 1 1960	1 015 00	
5 000	" " " " " " " " " "	5 031 64	
3 000	" " " " " " " " " "	3 040 00	
3 000	" " " " " " " " " "	3 000 00	3 000 00
5 700	U S A Treasury 3½s Oct 15 1945-43	5 225 00	
2 000	U S A Treasury 4s 1955-51 (Reg)	2 000 00	2 000 00
5 000	U S A Treasury 2s 1949-51	5 000 00	
3 000	U S A Treasury 2½s 1972-67 (Reg)	3 000 00	3 000 00
500	U S Treasury Note ½s Dec 15 1945	500 00	500 00
2 000	U S A Treasury ¾s Nov 2 1945	2 000 00	
35 000	U S A Defense Savings 2½s 1955 G		35 000 00
10 000	U S Treasury Ctf of Ind ¾s 1944		10 000 00
5 000	" " " " " " " " " "	5 000 00	
200	" " " " " " " " " "	200 00	
5 000	" " " " " " " " " "	5 000 00	
2 000	" " " " " " " " " "	2 005 63	
2 000	" " " " " " " " " "	2 005 63	
1 000	" " " " " " " " " "	1 022 50	1 075 00
1 000	" " " " " " " " " "	1 015 00	
3 000	" " " " " " " " " "	3 000 00	
25 000	Massachusetts Medical Service Demand 1955	25 000 00	25 000 00
		1 00	1 00
		5 167 70	
		5 751 92	
		6 43	
		1 074 48	1 074 48
		127 245 28	160 553 13
Cash	Total Securities	7 940 86	
	Merchants National Bank	8 606 46	93 73
	New England Trust Co		
	Total	143 797 60	160 553 13

SCHEDULE A EXHIBIT 4
BUILDING FUND DECEMBER 31 1943

Balance January 1 1943	6,921.30
Additions	
Income from Securities	1,776.44
Net Profit on Securities Sold	
Called or Matured	728.45
Total Additions	2,504.89
Balance December 31 1943	66,062.29

perfections which did not permit military service were found in 17 per cent. Such a rejection rate among doctors who have applied for commissions is about standard.

As can be seen, on the whole, older men have been retained as essential physicians and younger ones have gone into military service. Persons inclined to disparagement have suggested that too many young men are being declared essential by special interests. This thought is not borne out by this analysis. The curve of essential men bears an almost direct ratio to length of time from graduation. Older men are not considered available, and only a few younger men are considered essential. This general trend is unmistakable. It is believed to reflect the experience of the entire state.

It is difficult to perceive how many more practicing physicians can be withdrawn from their homes without serious difficulty to the civilian population. In fact, the work of your

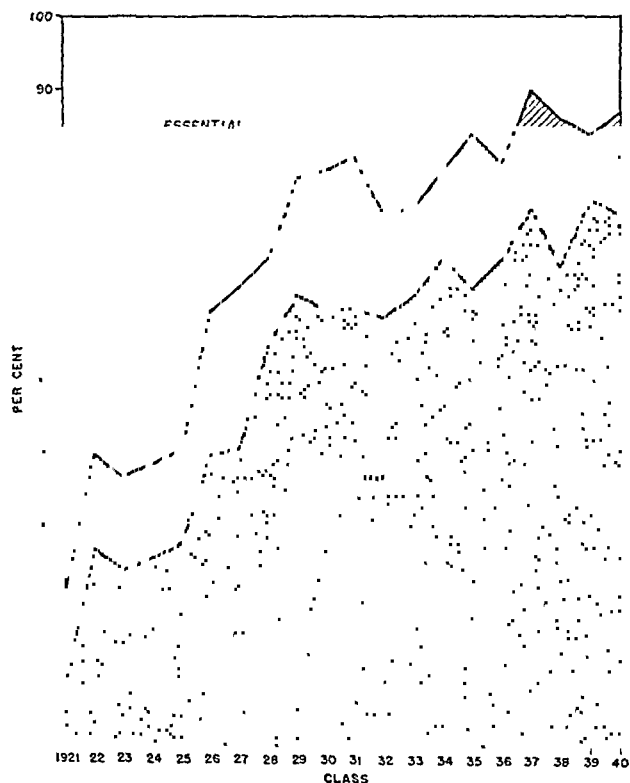


FIGURE 1. *The Classification of the Graduates of a Medical School Who Live and Practice in Massachusetts.*

committee is now becoming more and more concerned in attempts to place doctors in areas within the Commonwealth where the civilian population has come to consider itself medically shorthanded. The committee has been able to lend a helping hand in certain instances. In general, to keep accurate track of the medical migrations that are occurring is a difficult matter. Each local chairman is on the alert, however, keeping his eye on the situation within his district. At present, there is believed to be no serious medical shortage in any part of the Commonwealth.

The January 12 number of the *New England Journal of Medicine* gave an admirably succinct account written by the secretary of the Society of the recent change in policy regarding the awarding of commissions to graduates of substandard schools in Massachusetts who are licensed to practice here. A ruling from the Surgeon General's Office that prevents such men from receiving commissions in the future has caused a good deal of confusion. Many patriotic young men who hoped to obtain commissions on the completion of their internships were disappointed. In the main, such men have behaved extremely well. Many are continuing to serve as residents or interns in hospitals badly needing them, regarding such service as their contribution to the war effort. Others have opened offices in areas claiming to need physicians, and few, if any, have been drafted by Selective Service as privates.

The 9-9-9 plan for interns and residents has gone into effect commencing, as do so many new undertakings, with many

creakings. The establishment of a quota of interns in hospital approved for intern training appears to have enabled certain institutions to obtain a fairer share of this commodity than they did a year ago, although how satisfactorily is less certain. There seems to be developing a tendency for many hospitals to conserve a resident staff independent of the 9-9-9 plan by employing young physicians — women, foreigner or physically rejected men — who are not of potential use for military service. Thus, the hospitals of Massachusetts have asked for the deferment of but relatively few commission officers. The majority of deferment requests that were submitted before the deadline of November 15 were accepted by the Surgeons General. The first activation of this plan has appeared to yield reasonably promising results.

Bearing in mind the influenza epidemic of twenty-five years ago, your committee is formulating plans with the War Participation Committee by which a type of emergency medical service can be established in this state that will be called to reach any region where it might be needed at any time. Your committee also is working with the Commissioner of Public Health to systematize the relocation of physicians for civilian practice under Public Law 216, signed by the President on December 23, 1943. As the details of these two undertakings are perfected they will be appropriately announced.

HOWARD M. CLUT
EDWARD L. KICKHAM
DWIGHT O'HARA
WALTER H. PULSIFER
B. P. SWEENEY
REGINALD FITZ, *Chairman*

APPENDIX NO. 7

REPORT OF THE COMMITTEE APPOINTED TO CONSULT WITH REPRESENTATIVES OF THE OTHER NEW ENGLAND STATE MEDICAL SOCIETIES REGARDING THE WAGNER-MURRAY DINGELL BILLS

The initial conference with representatives of other New England state medical societies was held on September 2, 1943. At this conference, a great deal of wholesome discussion took place. Everybody had a chance to express his opinion and to express himself also as to the opinion of his respective colleagues in his own state. The consensus was that any criticism of proposed national legislation should be as constructive as we could make it and that flat-footed disapproval of the bill would be useless. Accordingly, the conference agreed to adjourn and to reconvene at a later date, and each member of the conference was asked to formulate some thoughts in the meantime.

In pursuance of this thought a second meeting was held on October 20 with the same group present except for the absence of Dr. Creighton Barker, of Connecticut. At this time, reports were made by all the members and, in particular, written reports were submitted from Rhode Island and Connecticut. At the close of the meeting the chairman was authorized to appoint a subcommittee to draw up a statement that could be submitted to the different medical societies for their approval. The chairman appointed Dr. James R. Miller, of Connecticut, and Mr. John F. Farrell, executive secretary of the Rhode Island Medical Society.

A third meeting was held on November 13. The prepared statement was read by Dr. Miller and Mr. Farrell and was gone over, sentence by sentence, in a long three-hour session. Not only was the subject matter very thoroughly discussed, but the exact wording of the sentences carefully scrutinized. Many changes and corrections were made in the original report. The statement was unanimously approved by all the members present and was agreed to also by the representative from Vermont, Dr. B. F. Cook, and by Dr. Barker, who were absent. It was agreed that this statement should be presented to the respective societies and if adopted by them, that it should be released to the press, to the *Journal of the American Medical Association* and the *New England Journal of Medicine*, and a copy sent to each senator and representative from New England. This statement was adopted by all the state medical societies of the New England states. Its language and structure has in no way been changed in its adoption. The statement is as follows:

MASSACHUSETTS MEDICAL SOCIETY
8 Fenway, Boston

December 2, 1943

Dear Sir:

junction with the medical
Island and Connecticut
Bill 2861 now before the
submits its views on this
proposed legislation.

We approve of the broad medical objective of the act that we interpret
to be an attempt to improve the health of the people. As a basis of our
approval we cite the progressive leadership which the physicians of New
England have always shown in the development of public-health enter-
prise for t
ary im
The
the federal government and already play a large role in the provision of

Private enterprises in the field of voluntary prepaid medical and hos-
pital care
This
New
the
hose
rious
we shall be glad to work out plans with representatives of the federal
and state governments to improve the health of all the people, but we
should expect that any plans that might be devised would take full ad-
vantage of existing agencies and be developed within the social patterns
that are well understood by our people.

Very truly yours,
[Signed] Roger I. Lee
ROGER I. LEE, M.D., President
[Signed] Michael A. Tighe
MICHAEL A. TIGHE, M.D., Secretary

This statement was sent as an open letter to Massachusetts
representatives in the Congress of the United States under
the authority of the Executive Committee, acting in the
name of the Massachusetts Medical Society.

WALTER G. PHIPPEN, Chairman

APPENDIX NO. 8

REPORT OF THE COMMITTEE ON CANCER

I transmit herewith majority and minority reports of the
Committee on Cancer together with enclosures—a copy
of the rules and regulations for state-aided cancer clinics as
of December 15, 1943, a specimen referral card to be issued
for the use of physicians sending cases to the clinics, and
an appendix embodying factual matter and opinions bear-
ing on that part of the regulations to which exception is
taken in the minority report.

I have felt it necessary to present a minority report because
of my conviction (1) that the propriety of final action upon
a question of public relations and economics by a committee
made up of technical experts in the field of cancer, most of
whom are affiliated with the cancer program of the Department
of Public Health, is questionable; (2) that a fee of ten
dollars (\$10.00) is unnecessary and not in the public interest,
and (3) that so much feeling has been aroused that an ex-
pression of the collective wisdom of the Council is desirable
either to support the action of the Department of Public
Health and thus strengthen the position of those of us who
conduct the clinics against local criticism or, on the other
hand, to influence the department toward correction of the
point of contention, which, though small in fact, is large
in principle.

REPORT OF THE MAJORITY

On November 3, a letter from the Commissioner of Public
Health, Dr. Vlado A. Getting, was received by the chairman
of the Committee on Cancer which read in part as follows:

As you no doubt know, the Department of Public Health
has, of necessity and in accordance with the laws of Massa-
chusetts, had to revise the regulations pertaining to the
cancer clinics. I should, therefore, appreciate an oppor-
tunity to appear before the Committee on Cancer at its
next meeting, in order to present these regulations to the
committee and to explain the reasons for their adoption
and the attitude of the department in this matter.

The request of the Commissioner was cordially received
by your committee and a meeting was held November 17,
1943, at the Harvard Club in Boston, all members of the
committee and the Commissioner being present.

At that time the Commissioner courteously explained the
circumstances making necessary the changes in methods
of administering the financial affairs of the state-aided clinics.

After the hearing the committee in executive session con-
sidered the regulations as amended. It was finally moved
by Dr. Simmons and voted:

The committee deploras the fact that changes have to
be made in the conduct of the state-aided cancer clinics
due to the interpretation of the Constitution of Massa-
chusetts by the Attorney General.

The majority of the committee believes that the regu-
lations presented are the best solution of the problem.

It recommends, however, that any action on these regu-
lations by the Council of the Massachusetts Medical Society
should be postponed for at least six months, so as to observe
the manner in which the clinics function under these new
regulations.

From this view, Dr. Ernest L. Hunt, chairman of the
committee, dissents.

FRANKLIN G. BALCH
CHANNING C. SIMMONS
PHILEMON E. TRUESDALE

REPORT OF THE MINORITY

The undersigned member of the committee, constituting
a minority, dissents from the opinion of the majority that
the rules and regulations as presented to the committee
"represent the best solution of the problem for the present."

The minority believes that the state-aided cancer clinics
should be operated within the obvious intent of the Con-
stitution (see "Appendix"), namely, that its services be lim-
ited to the indigent or near indigent, and if it is necessary to
exact fees from "such persons as may be in whole or in part
unable to support or care for themselves," such fees should
not be so large as to imply competition with private sources
of the same type of service and assistance, able to pay ten dol-
lars or over should.

The minority therefore reports be
accepted but that the recommendation of the minority be
adopted as expressing the opinion of the Council.

ERNEST L. HUNT, Chairman

NEW RULES AND REGULATIONS FOR CANCER CLINICS BY THE MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

The Cancer Clinic Regulations approved January 15, 1935, are hereby
rescinded and the following are substituted:

FOREWORD TO CANCER CLINIC REGULATIONS

Whenever possible, all patients shall be referred to the clinic by the
family physician, who may supply the clinic with the information re-
quested on the referral card, and who may furnish the clinic with in-
formation as to the patient's ability to pay in whole or in part the regular
clinic fee.

Refused patients will be returned for further diagnosis or treatment
to the family physician whenever the physician so requests.

CANCER CLINIC REGULATIONS

The Massachusetts cancer clinics are of two types: state cancer clinics
and state-aided cancer clinics.

A state cancer clinic is a medical unit furnishing consultation service,
diagnosis and treatment for persons suffering from precancerous con-
ditions, suspected cancer or cancer, "under the exclusive control, order
and superintendence" of the State Department of Public Health. This
type of clinic at present is held at Pondville and Weymouth.

A state-aided cancer clinic may be defined as a medical unit furnishing
either consultation service alone, or consultation service, diagnosis
and treatment, for persons suffering from precancerous conditions, sus-
pected cancer or cancer, "under the exclusive control, order and superin-
tendence, and from whom
such persons as may
be unable to support or care for themselves."

A committee composed of five or more physicians shall be appointed annually either by the local medical society or by the staff of a hospital. This committee shall be known as the cancer-clinic committee. The local organized medical group, through its cancer-clinic committee, may petition the State Department of Public Health to establish either a state cancer clinic or a state-aided cancer clinic. If a state cancer clinic is requested by the local group and approved by the department the cancer-clinic committee acts as an advisory body. If a state-aided cancer clinic is requested by the local group and approved by the department the cancer-clinic committee acts as an administrative body. The following rules and regulations apply to the state-aided cancer clinics:

The committee shall be responsible for all administrative matters pertaining to the clinic. These shall include the procurement of suitable quarters for the examination of the patients, preferably in a hospital, and the appointment and responsibility for the medical personnel, nurses, follow-up workers and clerical help of the clinic. Follow-up of cancer patients until death, and precancerous patients until the precancer is removed, and the maintenance of a uniform record system are required.

The committee shall make arrangements with the hospital in which the clinic meets to furnish examination rooms, instruments, diagnostic x-rays and other essential equipment and supplies.

At least three physicians should be present at each clinic session and shall preferably be a surgeon, a radiologist and a pathologist. If available, representatives of the various specialties shall be on call.

A nurse is to be in attendance at all clinics.

A clerical worker shall have charge of the clinic files and furnish such reports through the district health officer as may be requested. Uniform record forms will be supplied to the clinics.

Each clinic is to employ a "cancer clinic follow-up worker." This individual will attend to the follow-up and related duties of the clinic. In some of the smaller clinics it may be well, for purposes of economy, to combine the duties of the follow-up worker and the clerical worker. The minimum qualifications for the follow-up worker shall consist of some previous exposure to medical and social problems, as well as some knowledge of the medical and social resources available in the community.

When a problem arises which calls for advice from a medical social worker, unless the cancer-clinic follow-up worker is a trained medical social worker approved by the department, a request for aid should be sent to the local district health officer.

All new appointments of clinic personnel shall be subject to the approval of the department. The department reserves the right to approve on a temporary basis the appointment of personnel who do not meet the minimum qualifications, and to approve other changes in the clinic, during the war emergency.

Individuals able to pay will reimburse the clinic for services. The standard fee shall be \$10.00, which will include all routine and subsequent follow-up services, *except the services of the physicians of the clinic staff and certain other hospital services, which are gratuitous.* Individuals unable to pay \$10.00 but able to pay some fraction of that amount shall do so. The department will pay for services rendered by the clinics for "such persons as may be in whole or in part unable to support or care for themselves." Each clinic shall determine which individuals are "in whole or in part unable to support or care for themselves." Clinics in hospitals which do not have a prescribed form for determining medical indigency, and clinics in those hospitals whose method is not approved by the department shall adopt the department method. This consists of a personal interview with the individual by the admitting officer. Due care in selection of the admitting officer is of utmost importance.

In order to make the payments equitable for all clinics differing in size and services rendered the following procedure for payments has been adopted:

Each clinic shall submit monthly a list of services rendered the preceding month. Unit values have been determined for the ordinary services rendered by a cancer clinic. These are termed service units. The service units are totaled for each clinic and then converted into payment units. The payment units of all clinics, with the exception of those which, because of balances due to donations of clubs, individuals, community chest, legacies and other sources, do not need current payments, are totaled. The money available for the clinics for a given month is divided by this figure to determine the monetary value of a payment unit. This figure multiplied by the number of payment units for a given clinic minus the money received from patients who pay all or part of the \$10.00 fee furnishes the amount of clinic payment to be made by the State. In this way the State pays for none of the services to individuals who can pay for themselves and only for a part of the services of "such persons as may be in whole or in part unable to support or care for themselves," as both physicians and hospitals contribute materially to all groups.

The chief of each clinic shall furnish a monthly report, made under penalty of perjury, listing the units of work done by the clinic, the amounts received from patients who can pay all or a part of the \$10.00 fee, and the statement, "The clinic is billing the State only for the services rendered, to the best of our knowledge and belief, to such persons as may be in whole or in part unable to care for themselves." On the invoice submitted for payment the statement shall be appended, "This bill is submitted for payment of services only for 'such persons as may be in whole or in part unable to care for themselves.'"

If major changes in the management of a clinic are contemplated, the approval of the Department of Public Health should be obtained.

The Department of Public Health reserves the right to have its representative make regular inspections of the clinics and make suggestions for improved service. It may cease purchasing service from a clinic which fails in its obligations to the public.

When a clinic ceases to sell service to the State, either by a vote of the local group which originally sponsored it, or by a vote of the Department of Public Health, it is the responsibility of the department to follow the cancer patients previously seen at the clinic, until death. Arrangements must be made either with other clinics, district health units or voluntary agencies of the Advisory Cancer Clinic Committee, to see that this is done.

SERVICE UNITS	VALUE IN UNITS
New case	10
Return case	5
Special consultation	5
Gastrointestinal series	20
Other x-rays	10
Complete blood examination	3

Proctoscopic examination	1
Cystoscopic examination	2
Biopsy	3
Social service:	
Home visit	6
Office consultation	2
Telephone and correspondence	1
Transportation of patients	4

SERVICE UNITS	PAYMENT UNITS	PAYMENT U
Not over 40		30
Over 40 but not over 80		50
Over 80 but not over 120		70
Over 120 but not over 160		80
Over 160 but not over 200		90
Over 200 but not over 240		100
Over 240 but not over 280		110
Over 280 but not over 320		120
Over 320 but not over 360		130
Over 360 but not over 400		140
Over 400 but not over 440		150
Over 440 but not over 480		160
Over 480 but not over 520		170
Over 520 but not over 560		180
Over 560 but not over 600		190
Over 600 but not over 640		200
Over 640 but not over 680		210
Over 680 but not over 720		220
Over 720 but not over 760		230
Over 760 but not over 800		240
Over 800 but not over 840		250
Over 840 but not over 880		260
Over 880 but not over 920		270
Over 920 but not over 960		280
Over 960 but not over 1000		290
Over 1000		300

Approved by the Public Health Council, December 14, 1943.

SAMPLE OF PROPOSED REFERRAL CARD FOR USE OF PHYSICIANS SENDING CASES TO THE CLINICS

FRONT OF CARD

.....CANCER CL

Please admit.....

PLEASE CHECK:

1. Diagnosis only — patient to be returned to me. I do not desire social worker regarding patient.

2. Diagnosis and treatment,—clinic to make arrangements treatment.

PLEASE CHECK:

1. After treatment I desire social worker to follow up patient with consulting me.

2. After treatment I prefer that social worker will consult me seeing patient.

Signed

Address

REVERSE OF CARD

THE BEARER IS NOT IN THE POSITION TO PAY FOR PRIVATE CONSULTATION

1. He is able to pay full clinic fees.

2. He is able to pay partial clinic fees.

3. He is unable to pay any clinic charge.

Fees collected from patients are to pay in part for the maintenance of the clinic. The services of the physicians and those contributed by the hospital are gratuitous.

APPENDIX

New rules and regulations for the government of the state-aided cancer clinics were issued early in October, which contained the following provision for collecting fees from patients applying for clinic service:

Individuals able to pay will reimburse the clinic for services. The standard fee shall be \$10.00, which will include all routine diagnostic services and all subsequent follow-up services. Individuals unable to pay \$10.00, but to pay some fraction of that amount, shall do so. Department will pay for services rendered by the clinics for such "persons as may be in whole or in part unable to support or care for themselves." Each clinic shall determine which individuals are "in whole or in part unable to support or care for themselves."

Another paragraph further provided that the funds so realized should be applied toward the expenses of the clinics while the services of the medical staffs continue voluntary and gratuitous, thus in effect extending medical charity beyond the patients to the treasury of the Commonwealth.

On November 4, the Worcester Clinic Committee convened for the purpose of considering the new regulations, voted its disapproval of that section on the ground that the State Department of Public Health would be "obviously selling the services of physicians who themselves are donating their services" and asked for its clarification.

At the hearing before the Committee on Cancer on November 17, the Commissioner very courteously explained the circumstances making necessary the changes in methods of administering the financial affairs of the state-aided clinics. In brief, it appears that prior to the present commissioner's appointment to office certain legal opinions had been rendered to the effect that the method of financing the clinics through subsidies, which had been in practice since their inception, was illegal. Consequently a special act (House 1387) was passed by the Legislature validating all expenditures that had been made by the department in support of the clinics. A new plan was then set up by the department to purchase the services of the clinics for the patients and an elaborate system of unit values was devised and put into operation. The new plan was reviewed by the Attorney General's office and also declared to be illegal because it was in violation of Article XLVI, Section 3, of the amendments to the Constitution of Massachusetts, which section reads:

Section 3. Nothing herein contained shall be construed to prevent the Commonwealth, or any political division thereof, from paying to privately controlled hospitals, infirmaries, or institutions for the deaf, dumb or blind not more than ordinary and reasonable compensation for care or support actually rendered or furnished by such hospitals, infirmaries or institutions to such persons as may be in whole or in part unable to support or care for themselves.

As a result of these legal opinions the department considered that it had three possible alternatives for administering the clinics: they could be restricted to the service of the medically indigent only; they could be put on a fee basis and the doctors paid; or the clinic could serve the medically indigent gratis and collect fees from those able to pay.

The objection to the first plan was that cancer is not limited to the indigent, and it is the job of the department to fight cancer. To the second was the objection that if all clinic doctors were paid the funds available would not be sufficient. The third plan, which seemed to the Public Health Council most feasible, was consequently adopted and the maximum fee of ten dollars decided on and approved by the Attorney General.

The Commissioner then presented to the committee a revision of the regulations in which the paragraph under question was changed to read:

Individuals able to pay will reimburse the clinic for services. The standard fee shall be \$10.00 which will include all routine and follow-up services, except the services of the clinic staff and certain other hospital services, which are gratuitous. Individuals unable to pay \$10.00 but able to pay some fraction of that amount shall do so. The Department will pay for services rendered by the clinics for "such persons as may be in whole or in part unable to support or care for themselves." Each clinic shall determine which individuals are "in whole or in part unable to support or care for themselves."

The revision by dropping the word "diagnostic" and adding "except the services of the clinic staff and certain hospital services, which are gratuitous" aims to make it clear to the patients that the charges are only for the clinic overhead and not for the services of the doctors and nurses.

To further emphasize the fact of the gratuitous service of the medical staff, the Commissioner presented a revision of the referral card which physicians use in sending patients to the clinic in which the doctor is asked to certify that the patient is not able to pay for private consultation and to express his opinion as to the patient's ability to pay clinic fees. To this the Commissioner agreed to add in bold type the words:

Fees collected from patients are to pay in part for the maintenance of the clinic. The services of the physicians and those contributed by the hospital are gratuitous.

This aims to impress on both the referring doctor and the patient who brings in the card the fact that he is receiving gratuitous services from the medical staff of the clinic.

The Commissioner expressed the opinion that the fee of \$10.00 would act as a deterrent to abuse of the clinic staff charity. He also felt that the certification asked of the referring doctor to the effect that the bearer is unable to pay for private consultation or able to pay the clinic fee or certain fractions thereof or unable to pay anything would automatically eliminate the person able to pay \$10.00, who would naturally prefer a private consultant.

The majority of the committee concurred with the views of the Commissioner.

The minority contends that the section of the constitution quoted above clearly defines the group which is now comprehended by the term "medically indigent" as those for whom the state may properly purchase medical services. A device for extending medical service beyond the clear intent of the constitution strikes at the foundation of orderly and controlled government.

The present is a moment fraught with grave threats to the economic freedom of the medical profession. Throughout the land feeling runs high against further state and institutional encroachments on major fields of private medical practice. Any unnecessary aggravation of this feeling now is both untimely and unwise.

In many sections of the state a fee of \$10.00 is equivalent to the usual private consultation fee. To establish such a fee standard for clinic services, however it serves expediency, is of itself a clear bid for patronage by persons above the economic level of those unable or nearly unable to support or care for themselves and will tend to alienate the support of the medical profession from the cancer program and to embarrass the professional relations of those members of the clinic staffs who from loyalty to the program elect to continue in the work.

ERNEST L. HUNT, Chairman

APPENDIX NO. 9

REPORT OF THE WAR PARTICIPATION COMMITTEE

Late in the fall of 1943 the committee instructed its chairman to undertake a survey of the distribution of active practicing physicians in Massachusetts with particular reference to the number per thousand of population in the various districts, as well as in the Commonwealth as a whole. Accordingly, the district chairmen of the committee were instructed to prepare such surveys with the assistance of the local Procurement and Assignment committees. To date complete reports have been received from only six districts, namely, Barnstable, Bristol North, Hampshire, Worcester North, Middlesex East and Norfolk South—a disappointing number. Few reports of civilian doctor shortage, however, have come to the attention of this committee, and we believe that at the present time no emergency exists. Some relocation of physicians has been executed by the State Procurement and Assignment Committee at the request both of local communities and of individual doctors seeking a settlement; as of this date all major community requests have been satisfied. There has existed from the beginning the closest co-operation between our War Participation committees and the Procurement and Assignment committees on the district as well as on the state level.

At a meeting of the War Participation Committee on January 30, 1944, it was the consensus that plans should be entertained to meet the possibility of an outbreak of a serious epidemic of disease. In spite of the fact that there is no large area within the Commonwealth that is at present medically shorthanded, it was considered wise for the Society to be prepared for such an outbreak, when civilian needs for emergency medical care might become acute in several areas at the same time.

Various schemes were considered, prominence being given to the plan of the Worcester District Medical Society described by Dr. J. J. Dumphy in the *New England Journal of Medicine*, issue of January 7, 1943, and to the so-called "San Francisco Plan," both of which present certain features that

January	20	Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation	Burton E. Hamilton Louis Wolff	February	17	Burns and Reconstruction Surgery	Joseph H. Shortell Donald W. MacCollum Charles C. Lund Richard B. Cattell
February	17	Peripheral Vascular Disease	John Homans	March	16	Acute Abdominal Emergencies	
March	16	Fractures of Extremities	Carroll B. Larson	April	20	Cardiac Neuroses, Cardiac Emergencies and Cardiac Rehabilitation	
April	20	Pilonidal Sinus and Common Diseases of the Anus and Rectum		May	18	Chest and Abdominal Injuries	
May	18	Blood Dyscrasias and Transfusions		June	15	The Psychoneuroses and Their Management	
June	15	Contagious Diseases and Complications				STATION HOSPITAL, WESTOVER FIELD, CHICOPEE FALLS, MASSACHUSETTS	
		U. S. NAVAL HOSPITAL, CHELSEA, MASS.		November	18	Fractures of Extremities	G. Kenneth Coonse John D. Adams
November	18	The Skin	John G. Downing Francis P. McCarthy John J. Curry Samuel A. Levine Conger Williams	December	16	The Use of Penicillin and the Sulfa Drugs	Charles A. Janeway
December	16	Cardiac Neuroses, Cardiac Emergencies and Cardiac Rehabilitation		January	20	Chest and Abdominal Injuries	Horace K. Sowles Robert K. Brown Robert R. Linton Edward Hamlin, Jr. C. Guy Lane
January	20	Contagious Diseases and Complications	Edwin H. Place	February	17	Acute Abdominal Emergencies	
February	17	Fractures of Extremities	Russell F. Sullivan Albert B. Ferguson Maxwell Finland	March	16	The Skin	
March	16	The Pneumonias and Other Respiratory Infections		April	20	Contagious Diseases and Complications	
April	20	Burns and Reconstruction Surgery		May	18	Stomach, Biliary Tract and Intestinal Disorders	
May	18	Peripheral Vascular Disease		June	15	Acute Infections of the Central Nervous System	
June	15	Symposium on Physiotherapy				DISPENSARY, U. S. NAVAL CONSTRUCTION TRAINING CENTER, DAVISVILLE, RHODE ISLAND	
		STATION HOSPITAL OR LOVELL GENERAL HOSPITAL FORT DEVENS, MASSACHUSETTS		November	18	Chest and Abdominal Injuries	Richard H. Sweet Robert K. Brown Jerome J. McCaffrey (Providence, R. I.) Wilfred Pickles Jerome J. McCaffrey (Providence, R. I.) Richard Kovacs (New York City) Charles A. Janeway
November	18	Acute Abdominal Emergencies	Samuel F. Marshall Elmer C. Bartels Urban H. Eversole Rene J. Dubos and associates.	December	16	The Neuroses and the Wartime Fatigue Exhaustion Syndrome	
(Station)				January	20	Head, Spine and Nerve Injuries	
December	16	Tropical Diseases, Including Malaria and Other Insect-Borne Diseases	Donald Munro	February	17	Symposium on Physiotherapy	
(Lovell General)				March	16	The Use of Penicillin and the Sulfa Drugs	
January	20	Head, Spine and Nerve Injuries	Charles A. Janeway	April	20	The Pneumonias and Other Respiratory Infections	
(Station)				May	18	Cardiac Neuroses, Cardiac Emergencies and Cardiac Rehabilitation	
February	17	The Use of Penicillin and the Sulfa Drugs	John W. Strieder Edward A. Cooney	June	15	Blood Dyscrasias and Transfusions	
(Lovell General)						U. S. NAVAL HOSPITAL, NEWPORT, RHODE ISLAND	
March	16	Chest and Abdominal Injuries		November	18	Head, Spine and Nerve Injuries	Wilfred Pickles Jerome J. McCaffrey (Providence, R. I.) Edward J. West D. W. J. Bell (Providence, R. I.)
(Station)				December	16	Contagious Diseases and Complications	
April	20	Acute Infections of the Central Nervous System		January	20	Burns and Reconstruction Surgery	Edward A. Cooney Carroll B. Larson Ernest M. Daland Eugene E. O'Neil George Miller John Byrnes George C. Shattuck Rene Dubos and associates
(Lovell General)				February	17	Peripheral Vascular Disease	
May	18	Contagious Diseases and Complications		March	16	Tropical Diseases, Including Malaria and Other Insect-Borne Diseases	
(Station)				April	20	Symposium on Physiotherapy	
June	15	Cardiac Neuroses, Cardiac Emergencies and Cardiac Rehabilitation		May	18	Diarrheal Diseases	
(Lovell General)				June	15	Stomach, Biliary Tract and Intestinal Disorders	
		STATION HOSPITAL, CAMP EDWARDS, MASSACHUSETTS				AIR CORPS STATION HOSPITAL, NEW HAVEN, CONNECTICUT	
November	18	Symposium on Physiotherapy	Arthur L. Watkins	November	18	Joint Injuries	Samuel C. Harvey Malcolm S. Eveleth (New Haven, Conn.) Samuel C. Harvey (New Haven, Conn.) Samuel C. Harvey (New Haven, Conn.) Ralph E. Wheeler Francis C. McDonald (Boston) Arthur J. Geiger (New Haven, Conn.) Henry R. Viets
December	16	The Pneumonias and Other Respiratory Infections	Francis C. Lowell	December	16	Acute Abdominal Emergencies	
January	20	Acute Abdominal Emergencies	Robert R. Linton	January	20	Stomach, Biliary Tract and Intestinal Disorders	
February	17	Head, Spine and Nerve Injuries	Donald Munro	February	17	Diarrheal Diseases	
March	16	Diarrheal Diseases	Ralph E. Wheeler Francis C. McDonald	March	16	Acute Infections of the Central Nervous System	
April	20	The Use of Penicillin and the Sulfa Drugs		April	20	Tropical Diseases, Including Malaria and Other Insect-Borne Diseases	
May	18	Burns and Reconstruction Surgery		May	18	The Use of Penicillin and the Sulfa Drugs	
June	15	The Skin		June	15	The Pneumonias and Other Respiratory Infections	
		CUSHING GENERAL HOSPITAL, FRAMINGHAM, MASSACHUSETTS				COAST GUARD ACADEMY* AND NAVAL SUBMARINE BASE,† NEW LONDON, CONNECTICUT, AND FORT H. G. WRIGHT,† FISHERS ISLAND, NEW YORK	
January	20	Cardiac Neuroses, Cardiac Emergencies and Cardiac Rehabilitation	Paul D. White Mandel E. Cohen	November	18*	Burns and Reconstruction Surgery	J. Eastman Sheehan (New York City) Paul W. Vestal (New Haven, Conn.) Donald B. Wells Sidney S. Quarrier (Hartford, Conn.) Richard Kovacs (New York City) Louis K. Diamond
February	17	Acute Abdominal Emergencies	Samuel F. Marshall Merrill J. Nicholson Merrill C. Sosman S. Burt Wolbach Francis C. Newton E. Stanley Emery	December	16*	Symposium on Physiotherapy	
March	16	Stomach, Biliary Tract and Intestinal Disorders		January	20†	Blood Dyscrasias and Transfusions	
April	20	The Psychoneuroses and Their Management		February	24†	Contagious Diseases and Complications	William Bell Kalei K. Gregory (Providence, R. I.)
May	18	Pilonidal Sinus and Common Diseases of the Anus and Rectum					
June	15	Tropical Diseases, Including Malaria and Other Insect-Borne Diseases					
		U. S. MARINE HOSPITAL, BRIGHTON, MASSACHUSETTS					
November	18	Peripheral Vascular Disease	Reginald H. Smithwick				
December	16	Diarrheal Diseases	James Marvin Baty Ralph E. Wheeler Carl W. Walter				
January	20	Fractures of Extremities					

Month	Cardiac Neuroses	Cardiac	Paul D. White	Mandel E. Cohen
March	16			
April	20			
May	18			
June	15			

Note Unless otherwise noted the instructor's address is Boston

COMMITTEE PERSONNEL

Executive Committee

Dr W R chard Ohler *Chairman* Boston
Dr Leroy E Parkins *Secretary* Boston
Dr Samuel C Harvey New Haven Conn (Chairman Reg on C
m ttee)
Dr Alexander M Burgess Providence R I (Member Reg on ' Com
m ttee)
Dr Chester S Keefe Boston (Chairman Reg on I Comm ttee and

General Committee (consists of the above and the following)

Dr	Samuel H. Proger	Boston (Member Massachusetts Military Post graduate Committee)
Dr	Frank R. Ober	Boston (Member Massachusetts Military Post graduate Committee)
Dr	Gordon M. Morrison	Boston (Member Massachusetts Military
E		Military
E		Massachusetts
E		
E		Committee

Military and Naval Personnel

Headquarters First Service Command Boston

Headquarters First Naval District Boston

Rear Adm. al Richard H. Lynng (MC)
Capt. A. Warren Stearns (MC)

U S Coast Guard Boston

Dr Lee C Watkins Senior Surgeon USPHS
Dr William W Simmons Passed Assistant Surgeon (R) USPHS

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALIORY, M D, *Editor**

BENJAMIN CASTLEMAN, M D, *Acting Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 30131

PRESENTATION OF CASE

A twenty eight year-old housewife entered the hospital because of pain in the right hip

The patient was in apparent good health until about six years before admission, when, without antecedent trauma, she developed a dull ache in the right thigh and leg. The pain was not influenced by weather, but was aggravated by hard work and relieved by bed rest. It gradually increased in severity and the thigh became the area of maximal pain. About two years before entry, during the course of pregnancy, the pain became quite severe following successful delivery of a normal infant, the pain seemed to subside for a while. Gradually, however, it again increased in severity, although there were some symptom free days. She noted progressive limitation of activity so that by the time of admission she could not scrub the floor or climb more than one step at a time. She walked with a limp.

There was no history of tuberculous contact or of cough, sputum, hemoptysis, increased night sweats, chills, fever or urinary symptoms.

*On leave of absence

Physical examination showed a well developed, well-nourished woman in no distress. The heart, lungs and abdomen were normal. There was tenderness over the right ischial tuberosity and over the inferior iliac spine, and considerable spasm of the right hip muscles. Some atrophy of the right thigh muscles was present without any difference in the length of the two extremities. The right hip was painful on flexion past 95°. Flexion was limited to 100°. Because of pain, internal rotation was limited to 15°, and external rotation to 10°. Full extension was possible.

The blood pressure was 135 systolic, 85 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a white cell count of 11,200 with 78 per cent neutrophils. The hemoglobin was 13.6 gm per 100 cc. A blood Hinton test was negative. The sedimentation rate was 4 mm in fifteen minutes, 6 mm in thirty minutes, 13 mm in forty-five minutes and 19 mm in sixty minutes. The blood uric acid was 4.0 gm per 100 cc.

An x ray film of the chest was negative. X-ray films of the pelvis showed a number of round cyst-like areas of diminished density lying in the wall of the right acetabulum (Fig 1). These measured from 0.2 to 1 cm in diameter and were surrounded by a zone of increased density. There was also generalized increase in the density of the bone throughout the region of the right acetabulum. In the lower margin of the head of the right femur, where it joined the neck, there was a similar area of diminished density with surrounding reaction. The joint space was markedly narrowed superiorly, and there appeared to be some destruction of the wall of the acetabulum medially. The right femur was held in slight adduction. The left femur and the remaining bones of the pelvis were normal.

On the fourth hospital day, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. W. A. ROGERS: May we see the x-ray films?

DR. LAURENCE L. ROBBINS: This is the lesion as described, with areas of rarefaction scattered through the wall of the acetabulum and the head of the



FIGURE 1. Roentgenogram of Ilium.

femur, and apparently involving the upper portion of the neck of the femur. So far as I can see, the rest of the bones appear normal.

DR. ROGERS: In considering a joint condition, an orthopedist is by experience forced to consider all the possibilities because of the common lack of the typical for any given condition in the roentgenogram. One may say immediately from the history and the roentgenogram in this case that we are not dealing with a slipped upper femoral epiphysis. We are not dealing with Legg-Perthes's disease, nor are we dealing with congenital dysplasia of the hip. The radiographic appearances of each of these three diseases are sufficiently typical to justify their exclusion in this case.

I am impressed by the diffuseness of the sclerosis. In the iliac side of the joint the sclerosis extends

quite high and is not the typical subchondral type of sclerosis that we commonly associate with strain due to mechanical fault in the joint. I am also impressed by the cystlike areas of diminished density, and by the circumstance that these are of rather scattered distribution. This one is rather high which is not especially remarkable, but also along the upper portion of the neck of the femur there are cystlike areas of diminished density, which lie beneath the capsule of the joint, and one wonders what they are doing there. In cases of degenerative arthritis we see cystlike areas of diminished density in the roentgenogram, but they are usually limited to the head of the bone—not on the acetabulum side—and are closer to the joint. I am also impressed by the circumstance that there is evidence of destruction in the medial portion of the joint—that is, the vertical inner wall of the hip joint. The destruction is not confined to one side but is on both sides. In a degenerative arthritic process one would expect that the smooth line of the bone comprising the two sides of the joint would pass almost completely around the extent of the joint. In this case the line is sharply broken medially and is on both sides. The joint line is extremely thin. It is so narrow that it could be due to a traumatic arthritis with destruction of the articular cartilage from bad mechanics, or due to destruction of the cartilage, such as one might see in an infectious process, either acute or chronic.

In considering these punched-out areas, the narrowing of the joint line and sclerosis, one naturally wonders if the patient might not have had gout, but in gout there is usually no history of almost continuous pain, varying in degree, to be sure, but from day to day and in direct proportion to activity. In gout, as we all know, there is generally a story of attacks with remissions of relative comfort. Furthermore, the blood uric acid level was well within normal limits, and the patient was not febrile, nor was there a leukocytosis.

The question of rheumatoid arthritis must be faced, and one is immediately impressed on examining these films with the rather diffuse sclerosis rather than diffuse atrophy. The irregularity in the joint line in a rheumatoid condition can be localized to a limited portion, but it is usually less of an excavation, more fuzzy, and not so deeply penetrating. Furthermore, the sedimentation rate did not exceed normal. It was high normal to be sure, but not what one would expect with rheumatoid arthritis, and I gather from the history that this was a single-joint affair.

One must also consider, of course, the Neisseria joint, and not be deterred from that diagnosis by the sclerosis—at least this is true of the sacroiliac joint. The irregularity of the joint line, with destruction of the cartilage and even subchondral bone, and some irregularly punched-out areas in the joint are not inconsistent. The most conspicuous

feature of the Neisserian sacroiliac joint is diffuse sclerosis, which may extend back several centimeters on each side, and here we have, in a way, the picture of a Neisserian joint. She had had this, however, for six years, and she had a range of motion from normal extension to 100° of flexion. She had definite internal rotation of 15°, which is within normal limit, and 10° of external rotation. One would think that, in a Neisserian joint of six years' duration, the motion would be considerably less free than it was in this case. Pain was a conspicuous feature, and although an acute Neisserian joint is something to be reckoned with from the standpoint of pain, after six years one would expect a rather quiescent, relatively immobile, if not actually fused, joint.

The streptococcus and staphylococcus have to be considered, but by and large one is not inclined to follow up that line of thought because there is no dislocation, there is no extensive lesion of the head of the bone, and the joint line is smooth on top; these are strongly against such a lesion, although a low-grade infection by either might produce this picture. Furthermore, most streptococcal or staphylococcal hip joints are fulminating affairs.

We must always consider tuberculosis in a chronic joint, and there are many features in this case that suggest this diagnosis. If this were a shoulder joint, it would be extremely likely. The shoulder joint being a nonweight-bearing joint, is not subjected to as much strain as the hip is, especially in women, and one might conclude that this was a caries sicca in the humerus and scapula. There are various irregularities about the joint, with extensive sclerosis, the destruction of the joint line is likewise in accord with a chronic, destructive, infectious process, which could be tuberculosis. The old concept that tuberculosis is a purely destructive disease from the standpoint of bone changes is not tenable. Areas of diffuse sclerosis of bone are extremely frequent, especially in the vertebral bodies, where sclerosis has been demonstrated to be the result of local anemia of the bone, the anemia resulting from thrombi that form in the local arterioles. With lessened blood supply the usual bone response is sclerosis.

We then come to a consideration that must be taken seriously — traumatic arthritis of the hip joint. The history does not contain a record of antecedent trauma. That does not mean, of course, that such trauma had not occurred. In dealing with joints, it is not uncommon to get a history similar to this one with respect to trauma, only to discover that one is dealing with a traumatic arthritis. By putting it up a bit more forcibly to the patient, trauma that had slipped the memory is often recalled. The prompt recovery from such trauma in adolescence is to be expected, followed by a slowly progressing degeneration of both sides of the joint.

In summary, I have seriously considered a Neisserian joint, a tuberculous joint and a traumatic

arthritic joint, nonrheumatoid and nonconstitutional, of course. My first choice, based on the diffuse sclerosis, the joint destruction and the presence of cystlike areas over an extensive zone, is tuberculosis. My next choice is traumatic arthritis.

DR. BENJAMIN CASTLEMAN: Dr. Smith-Petersen, will you tell us what you thought before operation and what you found at operation?

DR. MARIUS N. SMITH-PETERSEN: Our pre-operative diagnosis was low-grade infection in the anterior third of the ilium, directly above the acetabulum and in the roof of the acetabulum, with secondary synovitis of the joint itself and possibly with strain, secondary to faulty position of the hip — in other words, traumatic arthritis. The cystic areas that appear to be in the head of the femur and that seem to be due to bone atrophy are misleading. We were able to demonstrate these cysts at the time of operation, and they were actually in the acetabulum.

At the time of operation the roof was excised and the lower cystic areas cut across, releasing cheesy, putty-like material. The outstanding features of the joint itself were the many villi, particularly in the anterior portion of the joint. These villi were firm and dark brown, and when cut across, were fibrous in character. They were firmer than the villi commonly seen in villus arthritis or traumatic arthritis, but since the duration of symptoms was six years, we came to the conclusion that this was an old synovitis with villus formation, the recurring synovitis having become increasingly fibrous in character. The postoperative diagnosis was simply a villus condition of the synovia, with cysts of unknown origin in the anterior third of the ilium.

CLINICAL DIAGNOSIS

Multiple cysts of ilium, due to low-grade infection, with secondary synovitis.

DR. ROGERS'S DIAGNOSIS

Tuberculosis of hip?
Traumatic arthritis?

ANATOMICAL DIAGNOSES

Pigmented villonodular synovitis of right hip.
Osteoarthritis of right hip.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: As Dr. Smith-Petersen has said, all these villi were reddish brown and firm. On microscopic examination they showed a marked increase in the stromal cells, numerous giant cells of the foreign-body type and large deposits of hemosiderin within the phagocytes and within the stromal cells (Fig. 2). In some areas the tissue was made up of so-called "foam" or xanthoma-like cells — that is, phagocytic cells filled with fat. Nowhere was there evidence of tuberculosis.

On the fourth hospital day, an operation was performed.

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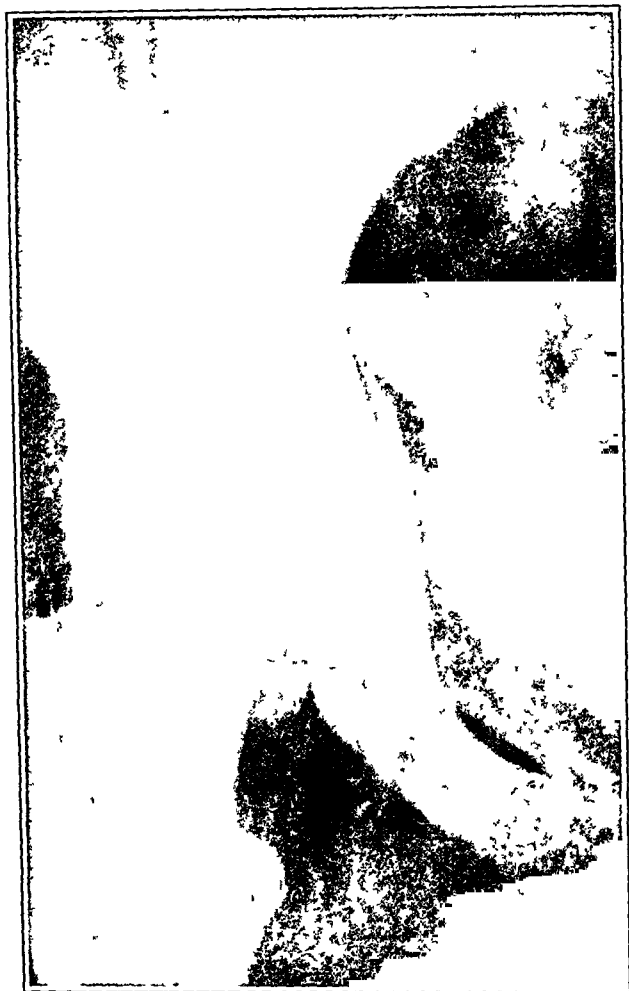


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lost about 25 pounds over a period of three years. Her appetite had been good. The past history was otherwise negative.

Physical examination showed a well-developed, well-nourished woman without any evidence of recent weight loss. She spoke in a whisper and was in no distress. The neck veins were distended, particularly on the left. The left supraclavicular fossa appeared fuller than the right, but no masses were palpable. The lungs were clear and resonant

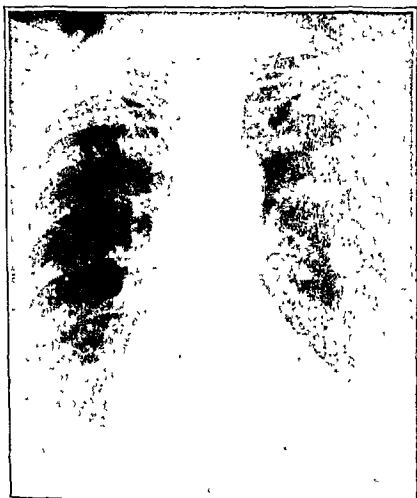


FIGURE 1.

throughout. The heart was enlarged to 2 cm. to the left of the midclavicular line in the fifth interspace. The sounds were of good quality and regular. A blowing systolic murmur was heard all over the precordium. The liver was palpable two finger-breadths below the right costal margin and was slightly tender. Superficial varicosities were seen over the abdomen and the lower extremities. There was no edema. Neurologic examination was negative except for a slightly diminished pharyngeal reflex and deviation of the tongue to the left. Repeated laryngeal examinations revealed the left vocal cord to be immobile and in the cadaveric position. No masses, ulceration or tubercles were seen on the cords or the subglottis. The arytenoids appeared normal and fairly movable.

The blood pressure was 130 systolic, 70 diastolic. The temperature was 100°F., the pulse 80, and the respirations 20.

Examination of the blood showed a red-cell count of 3,500,000, with 10.5 gm. of hemoglobin. The white-cell count was 6450. The urine was normal. A blood Hinton test was negative. The stools were negative.

An x-ray film of the chest (Fig. 1) showed a rounded area of increased density in the anterior portion of the left upper lobe at the level of the second rib. The heart was not enlarged. There was no definite widening of the aorta or evidence of aneurysm or a mediastinal tumor. A swallow of barium passed through the esophagus without hesitation at any point. An x-ray film taken two weeks later revealed a slight decrease in the size of the area of increased density. The left half of the diaphragm was somewhat elevated, but both leaves moved fairly well on respiration and there was no paradoxical motion.

A tuberculin test in dilution of 1:100,000 was positive. The venous blood pressure in the antecubital veins at the level of the sternomanubrial junction was equivalent to 7.2 cm. of water on each side. Repeated sputum examinations for tubercle bacilli were negative. An electrocardiogram showed normal tracings. The temperature remained about 100°F.

The patient did not seem to have much pain. Her voice improved transiently following laryngoscopic examination. She was discharged and told to return in four weeks for re-evaluation of her symptoms.

Second admission (two and a half months later). Following discharge the patient continued to have pain in the anterior chest and between the shoulder blades. She presented herself in the Out Patient Department about four weeks following discharge and was found to be fibrillating. An x-ray film of the chest showed no change from the previous examinations. During the next four or five weeks her condition gradually became worse, the pain increasing in severity. She had considerable cough, with dyspnea and occasional palpitation. The sputum was blood tinged. She had been given 1 gr. of digitalis every four hours for some weeks without apparent change. About one week before re-admission a scheduled bronchoscopy was postponed because she was fibrillating at a rate of 140, without noticeable dropped beats. She was given three doses of 2 cc. of Cedilanid within twenty-four hours and 1½ gr. of digitalis daily. Thereafter she continued to fibrillate, but at a rate of 100. Her condition otherwise remained essentially the same.

Physical examination on admission showed the diaphragm to be high on the left. Resonance was diminished over the left upper lobe posteriorly. Coarse rhonchi were heard throughout the chest, with stridor. The heart was slightly enlarged. The apical first sound was rough. The heart was fibrillating at a rate of 88, without a deficit. There was slight ankle edema.

The temperature was 100°F., the pulse 88, and the respirations 25. An x-ray film of the chest (Fig. 2) showed considerable fluid in the left pleural cavity. There was also density extending upward and outward from the hilus into the left upper lung field. The heart and mediastinum were displaced to the right.

The day after admission she was bronchoscoped. The left main bronchus was almost completely occluded by a mass arising in the lateral and anterior walls, leaving a 1-mm. opening. The mass was slightly irregular and reddish. A biopsy from the lateral wall was followed by an immediate massive hemorrhage, and 1500 cc. of blood was lost before

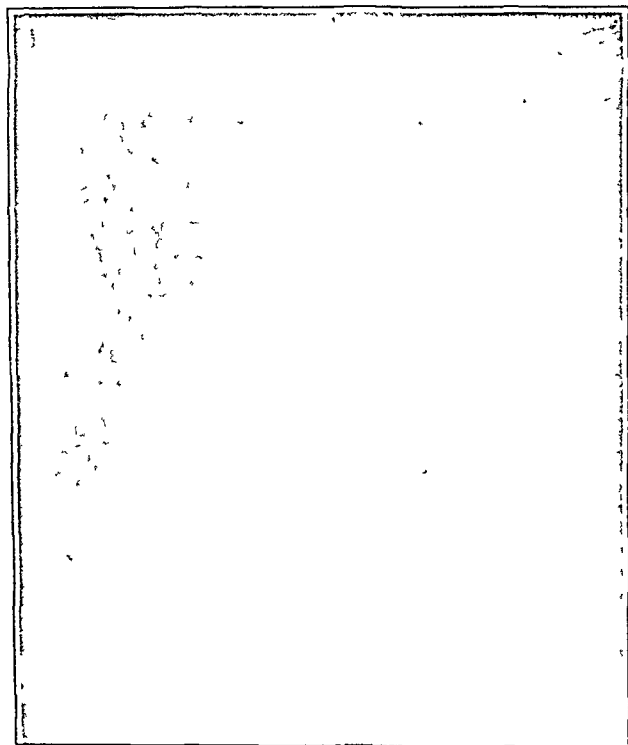


FIGURE 2.

it could be stopped. The pulse and blood pressure became imperceptible, but returned with the cessation of bleeding. She was given several transfusions and intravenous fluids. Examination following this episode showed dullness and flatness below the level of the sixth dorsal vertebra on the left posteriorly, with diminished breath sounds and many coarse tracheal bubbles throughout. The heart was fibrillating at a rate of 140, with a pulse deficit of 20. Pathological examination of the specimen revealed no diagnostic abnormality. Three chest taps in the course of the next eighteen days yielded about 700 cc. of bloody fluid. No micro-organisms, including acid-fast bacilli, or tumor cells could be found in the sediment. The fibrillation continued, the temperature ranged about 100°F., and she had considerable cough productive of a large amount of blood-streaked sputum. She went progressively down hill and on the twenty-first hospital day had sudden respiratory difficulty, accompanied by profuse sweating. She died a few minutes later.

DIFFERENTIAL DIAGNOSIS

DR. PAUL ZAMECNIK: If we summarize all the apparently pertinent findings at the time of the first admission, we find that they point to the region of

the arch of the aorta or to the left main-stem bronchus. In the first place the patient complained of difficulty in speaking, and we note that she had paralysis of the left vocal cord, which is consistent with paralysis of the left recurrent laryngeal nerve. Then she had cough, and fullness in the right supraclavicular region, and the neck veins were more distended on the left than on the right. She had pain in the sternum and between the shoulder blades. Finally, an x-ray film of the chest showed a rounded area of increased density in the anterior portion of the left upper lobe at the level of the second rib.

I wonder if we may see the x-ray films.

DR. MILFORD SCHULZ: These are the films made at the time of the first admission. You can see the indefinite area of increased density in the left upper chest. Whether that is infiltration or atelectasis, I do not know. The left leaf of the diaphragm appears to be elevated. Incidentally, the protocol did not mention it, but on fluoroscopy there was paradoxical motion.

DR. ZAMECNIK: But the diaphragm did move?

DR. SCHULZ: Yes. You can see a fair left main-stem bronchus on the oblique film. The impression was that the lesion had regressed, which I believe is partially due to technical difference in the films.

These films made at the time of the last admission show a marked change; the area of density has greatly increased.

DR. ZAMECNIK: How about this area?

DR. SCHULZ: It looks like a mass in the left mediastinum. In this film of the chest there is a large amount of fluid on the left side and a curious nodulation throughout the entire right lung field, not present previously.

DR. ZAMECNIK: Would you like to say anything more about these abnormalities? Do they look like metastatic disease?

DR. SCHULZ: They could be due to metastatic disease, but there are several other possibilities.

DR. ZAMECNIK: In attempting to explain the patient's downhill course and the cause of her death, let us focus our attention first on the most important single piece of information available — the findings of the bronchoscopic examination. "The left main bronchus was almost completely occluded by a mass arising in the lateral and anterior walls, leaving a 1-mm. opening. The mass was slightly irregular and reddish."

If we eliminate aneurysm as a cause of this woman's difficulties, we can confine our attention to tuberculosis and neoplastic diseases. The negative Hinton reaction, the lack of hypertension, the absence of an aortic diastolic murmur, the lack of pulsation in the sternal notch, the inability of the X-ray Department to find widening of the aorta and the unlikelihood that an aneurysm would produce such a localized invasion of the anterior and lateral bronchial walls make aneurysm a remote possibility.

The tuberculin test was found positive in 1:100,000 dilution. This reaction is interpreted as evidence that a person harbors a tuberculous lesion somewhere in the body, but it does not determine whether the lesion is active or healed. Certainly the x-ray picture of the chest is not suggestive of tuberculosis, unless it is a tuberculoma, which seems to be too rare a bird on which to pin a diagnosis in the face of data suggesting neoplastic disease.

One may divide neoplastic diseases into two groups, benign and malignant. Among the benign tumors of the lung and mediastinum are: dermoid cyst, neurofibroma, lipoma, adenoma and chondroma. The first three arise in the mediastinum and it is unlikely that they would invade a bronchus; the last two might arise in a bronchus. All these are relatively slowly growing tumors, which ordinarily produce pressure symptoms for months or years before becoming serious problems. The disease under discussion, on the other hand, was a rapidly progressive one. The fever, anemia and pleural effusion fit a little better with a malignant neoplasm of the chest than they do with a benign lesion.

The malignant diseases of the chest include lymphoma, carcinoma, sarcoma, teratoma and metastatic carcinoma or sarcoma. The mass seen by bronchoscopy appeared to arise near the left main-stem bronchus. Primary carcinoma of the lung is a frequent disease, accounting for 5 to 10 per cent of all deaths from cancer. In about 75 per cent of the cases, the original site is one of the main-stem bronchi. Except for the negative biopsy, therefore, the picture is a classic one for bronchiogenic carcinoma.

Metastatic carcinoma is, to be sure, an even commoner disease, but the metastases are usually, although not always, found in the periphery of the lung, and are often multiple. Furthermore the site of origin is usually the source of other signs and symptoms of the disease, which are absent in this case. There is therefore no advantage in choosing metastatic carcinoma over primary carcinoma, and there are definite disadvantages in such a selection.

Lymphoma is a great imitator, but the absence of splenomegaly (the spleen is not mentioned in the history), of peripheral adenopathy and of a symmetrical mediastinal enlargement deprives it of any positive support. Teratoma is a rare disease that is statistically unsound to diagnose, unless there is x-ray evidence of bone or tooth formation within the tumor mass. Primary sarcoma of the lung is likewise rare.

In summary, then, the evidence is consistent with the diagnosis of bronchiogenic carcinoma of the left main-stem bronchus, with mediastinal invasion causing paralysis of the left recurrent laryngeal nerve, and with pleural invasion. The cause of the fibrillation can be explained in one of two ways. First, it may have been due to the strain imposed on an aging heart by a severe anemia, or second, it

may have been due to infiltration of the pericardium and cardiac musculature by neoplastic disease.

DR. AUSTIN BRUES: I saw this patient for the first time when she was in shock following the bronchoscopy. For obvious reasons, most of which Dr. Zamecnik has given, it seemed that the lesion was probably a neoplasm and most likely carcinoma.

She was referred to the X-ray Department for an opinion whether, when she was in better condition, she might not get some x-ray therapy on the chance that this was a radiosensitive lesion. As I remember it, the radiologist who was consulted made the sensible observation that if this were tuberculosis it would probably be the wrong thing to do. We therefore made an effort to rule out tuberculosis and succeeded in doing so only by getting a considerable number of negative examinations for tubercle bacilli.

DR. HELEN PITTMAN: I saw the patient in the Out Patient Department when she came in complaining of shortness of breath and with a story of continued blood-spitting. I decided that all the signs added up to a bronchial neoplasm and referred her for the bronchoscopy that nearly exsanguinated her.

CLINICAL DIAGNOSIS

Carcinoma of lung.

DR. ZAMECNİK'S DIAGNOSES

Carcinoma of lung, left main-stem bronchus, with extension to mediastinum and pleura.

Auricular fibrillation due to anemia or metastatic carcinoma of pericardium or myocardium.

ANATOMICAL DIAGNOSIS

Epidermoid carcinoma of lung, left main bronchus, with metastases to mediastinal lymph nodes, pleura, pericardium, right lung and liver.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASRLEMAN: The autopsy on this woman showed that the lesion seen through the bronchoscope was a carcinoma that had extended into the lung for quite a distance and had infiltrated the left side of the mediastinum, completely surrounding but not invading the ascending aorta, part of the arch, with its branches, and the superior vena cava. The left recurrent laryngeal nerve was deeply imbedded in the tumor. The tumor had also extended along the lymphatics of the pericardium. Many small neoplastic nodules were present on the visceral pericardium, and a few were found on the parietal layer. The pericardial cavity contained 500 cc. of bloody fluid, as Dr. Zamecnik suggested. The arrhythmia may have been due to the pericardial involvement; the myocardium was normal. There were metastases to the liver and to the right lung. The recent lesions on the right side observed in the last roentgenograms were lymphatic metastases. The tumor was epidermoid carcinoma.

One interesting point in the history was the hoarseness. If one can rule out aneurysm, as Dr. Zamecnik did, the most frequent cause of hoarseness associated with a mediastinal lesion is carcinoma, rather than the other types of malignant disease. Lymphoma, for instance, frequently surrounds the recurrent laryngeal nerve but rarely infiltrates sufficiently to produce hoarseness. Would you agree to that, Dr. Aub?

DR. AUB: I have never observed hoarseness in a case of lymphoma.

DR. EDWARD B. BENEDICT: I have seen it once with tuberculosis.

DR. WILLIAM BECKMAN: How do you account for the fact that the patient's voice improved temporarily?

DR. BRUES: I do not know that she ever fully recovered her voice.

Was this a radiosensitive tumor?

DR. CASTLEMAN: The epidermoid carcinomas respond moderately well — not so well as the oat-cell carcinomas, but much better than the adenocarcinomas.

DR. ZAMECNIK: Was the phrenic nerve involved?

DR. CASTLEMAN: No.

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CARTHAGO DELEND A EST

WHEN Joshua blew his trumpets before Jericho, according to a source of information usually considered reliable, the walls came tumbling down. Troy went up in flames after the fifth column of the Greeks had penetrated its inner defenses. Nineveh and Tyre became one with the pomp of yesterday, and the merciful jungle has crept in to cover the bones of many an ancient city. After the second Punic War, when Hannibal had finally been driven from Italy, the elder Cato had only one ending for his speeches: *Carthago delenda est* — Carthage must be destroyed; and eventually that city, which had threatened the security of Rome, was erased from the map so thoroughly that corn could be planted over its ruins.

History repeats itself. Germany, for a century the scourge of Middle Europe, had prepared herself and had every intention of waging a destructive warfare on her European neighbors, if not on all the world that resisted her. Warsaw was destroyed. Rotterdam was laid waste in cold cruelty, after its surrender; the same would have happened to the cities of England if Goering had not overestimated the power of the *Luftwaffe*.

After years of desperate heroism the tide has turned, and it is the nations allied against Germany that have the mounting air power to destroy the cities of that rebellious nation. Berlin is being laid waste, and the job will be carried through to the finish. A moral question is now being raised, and many shocked persons, here and in England, are crying out against the violence and the mercilessness of this growing counterattack. We must not put ourselves in the category of those who make war on civilian populations, they say, and vengeance belongs to the Lord. (There is an equally applicable aphorism that those who live by the sword must perish by the sword.) That able commentator, Raymond Gram Swing, has taken occasion to answer these horror-stricken protestants: in the destruction of Berlin we are not primarily making war on her civilian population, on her women and children, but we are seeking to destroy Germany's power to make war against the world.

These pacifistic peacemakers are not the only ones who have feelings of guilt over the course the war has taken; millions of us have feelings of remorse. But they are not concerned with the destruction of Berlin; they are over our failure in the past to have taken the obvious steps necessary to prevent this war from breaking out at all. They are because we failed to prevent Japan from taking Manchukuo; because we failed to protect Ethiopia from Mussolini; because we failed to save Czechoslovakia from Hitler in 1938. These are the misdeeds that we should repent — to have failed then to use force in order to prevent this violence now.

CONTROL OF CANCER

MASSACHUSETTS has always been a pioneer in public-health matters, and through the efforts of

seventeen years, ably assisted by the medical profession of the Commonwealth, as well as by the Committee on Cancer of the Massachusetts Medical Society, which was appointed in 1917, the adjusted mortality rate for women from this disease in Massachusetts has shown a distinct drop, which is not the case throughout the country.

The program of the Department of Public Health consists of educational campaigns, a pathological diagnostic service, research work, cancer clinics and the maintenance of two hospitals adequately staffed and prepared to treat the disease by all known modern methods.

The federal government is also interested in the control of the disease. The United States Public Health Service is co-ordinating the activities of the various cancer programs in the country and, in addition, supplies radium to certain hospitals and conducts extensive research work in the National Cancer Institute at Bethesda, Maryland.

The American College of Surgeons has devoted much effort in stimulating the establishment of cancer clinics, in surveying and improving existing cancer clinics and in preparing uniform records. It has established a minimum standard for the conduct of these clinics, which are modeled after those inaugurated in Massachusetts.

The American Society for the Control of Cancer, established thirty years ago, has been a leader in the campaign against this disease. It is active in states not having an adequate cancer program, and in certain other states it supplements the work of public-health or other organizations carrying on a campaign for the control of the disease.

The sinister nature of cancer in its late stages is everywhere recognized, but much still remains to be done to convince the general public that periodic examinations by a physician comprise one of the most useful methods for the control of cancer. The present war provides no excuse for lessening the anti-cancer fight, and it is to be hoped that members of the medical profession will continue to educate their patients and the public at large concerning the value of the early recognition of suspicious symptoms by means of regular physical examinations. Furthermore, this effort should be redoubled during April, which has been designated "Cancer-Control Month" by a proclamation of the President.

MEDICAL EPONYM

GRAWITZ TUMOR

"Die Entstehung von Nierentumoren aus Nebennierengewebe [The Origin of Renal Tumors from Adrenal Tissue]" is the title of a paper read by Paul Grawitz (1850-1921), then assistant in the Pathological Institute in Berlin, on April 17, 1884, at the Thirteenth Congress of the Deutsche Gesellschaft für Chirurgie. This paper was published in the *Archiv für klinische Chirurgie* (30:824-834, 1884). A portion of the translation follows:

I shall try to show that such fetal anomalies not only occur, but do so with a frequency that exactly corresponds with the frequency of accessory strumas; then I shall explain the location of the strumas from the location of this sort of supernumerary bits of adrenal tissue; then, from the microscopic appearance controvert the assumption that the urinary tubules can be the matrix of the tumors; and finally, demonstrate the correspondence of these strumas with such growths, which quite evidently have originated from the adrenal glands.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

STONE — Ralph E. Stone, M.D., of Beverly, died March 22. He was in his sixty-seventh year.

Dr. Stone received his degree from Harvard Medical School in 1905. He was a member of the staffs of the Beverly Hospital, the Cable Memorial Hospital, Ipswich, and the North Shore Babies Hospital, Salem, and was consultant physician for the New England Industrial School for the Deaf. He was a member of the Massachusetts Medical Society, the American Medical Association, the National Tuberculosis Association, the Beverly Chamber of Commerce and the Harvard Club of the North Shore.

His widow survives.

CORRESPONDENCE

THE MUSE AND BOOK REVIEWS

To the Editor: The following seems apropos:

Let's have done with anonymity —
Book Reviewer, sign your name!
Naught writ of honest scrutiny,
Can enkindle mutual shame.

For if your stuff is worthy to be
called first rate, 'tis felt,
At least an author should be shown
just how your name is spelt.

No; don't steal up behind a man
who dares his toil undim;
For praise or blame, oblivion, fame,
Stand up in front of him!

ALBERT EVANS

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PERFORATION OF THE ILEUM FOLLOWING LATE ILEOSTOMY FOR ULCERATIVE COLITIS*

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BOSTON

THE treatment of intractable, chronic, non-specific ulcerative colitis by surgery in the form of ileostomy has been advocated in recent years by many surgeons as a means of arresting the disease. McKittrick and Miller,¹ Lahey,² Cave,³ Jones⁴ and others have reported marked success with this operation, but each has been careful to point out that when employed in the terminal stages, ileostomy is accompanied by an extremely high mortality rate. The present paper is a report of 2 cases illustrating a hitherto undescribed complication of late ileostomy for ulcerative colitis.

Both cases presented are similar in that death was due to generalized peritonitis following perforation of an ulcerative lesion of the ileum. In each case the perforation occurred above the site of ileostomy, the points of perforation being 15 and 6 cm., respectively, above the ileostomy openings. Grossly, the terminal ileum in each case showed a diffuse ulcerative process similar to that seen in the colon. The ulcers in the ileum were sharply demarcated and varied in size and shape, and the intervening mucosa was swollen. Microscopically, the mucosa was absent or necrotic, and there was edema and thickening of the submucosa, together with marked polymorphonuclear leukocytic and lymphocytic infiltration of the submucosa and of the mucosa at the ulcer edge. In the deep ulcers there was similar leukocytic infiltration of the muscularis. The pathologic findings, in other words, were identical with those found in the colon in chronic ulcerative colitis.

Because of the frequency with which the disease process extends into the terminal ileum in the later stages of the disease, the question arises whether in the present cases the disease process did not exist in the ileum above the site elected for enterostomy

at the time of operation. This question is reasonable because in each case ileostomy was performed close to the ileocecal valve. Certainly the perforations were not related directly to the ileostomies, since these patients lived seven weeks and eight and a half weeks, respectively, after operation.

Supportive evidence that disease existed proximal to the site of ileostomy before operation in each of these patients was the early postoperative course, for the ileostomy drainage never became solid but remained liquid and profuse. This was in marked contrast to the early postoperative course of other treated patients who survived, for in these cases the drainage began to solidify by the end of the second postoperative week. In addition, in Case 2, old healed ulcers were found in the terminal ileum above the ileostomy at autopsy.

Extension of nonspecific ulceration of the terminal ileum in patients suffering from chronic ulcerative colitis is fairly well known but has not received sufficient emphasis. In order to determine the frequency of this lesion in the ileum, 16,500 consecutive autopsies from the files of the Mallory Institute of Pathology, Boston City Hospital, were reviewed. Including the present cases, there were 44 cases in which chronic ulcerative colitis was considered to be the primary cause of death. In 17 of these, or 39 per cent, there was involvement of the small intestine. In the majority of cases the ulcerative process was confined to the terminal ileum—that is, to the lower 30 cm. of the ileum. In 3 cases, however, the ulcers extended throughout the lower third of the ileum. The incidence of perforation was striking. There was perforation of the colon in 7 cases (16 per cent), whereas perforation occurred in lesions of the small intestine in the 2 operative cases described and in 2 other cases in which fistulas developed from ulcers in the terminal ileum and jejunum. In other words, the incidence of perforative lesions of the small bowel in cases in which there was ulcerative ileitis was 24 per cent, or one and a half times greater than the incidence of perforative lesions of the large bowel.

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It is evident from a study of this material that the danger of perforation in the terminal ileum is always present in cases of severe ulcerative colitis in which surgery is delayed. To reduce the danger of this complication it seems wise always to do an ileostomy at least 90 cm. above the ileocecal valve and to avoid operative procedures on the terminal ileum. If a low ileostomy has been carried out and the fecal discharge remains loose and profuse, the possibility of ulceration of the terminal ileum above the ileostomy should always be kept in mind so that if acute abdominal symptoms develop, operative intervention can be immediately instituted. It should be possible in selected cases to visualize the terminal ileum before operation by barium and so to anticipate this complication.

CASE REPORTS

CASE 1. F. W. (B.C.H. 772,645), a 50-year-old, married man, was admitted to the medical service on January 8, 1935, complaining of rectal bleeding and frequent bowel movements. Three weeks before entry he began to have two to six bowel movements each day. The stools were loose and contained moderate amounts of bright-red blood. He was treated by his family physician with relief of symptoms, for 10 days. Three days before coming to the hospital, however, the symptoms returned in their original intensity and, in addition, there occurred gripping pains in the lower abdomen. On the day of entry, the patient felt weak and fainted twice. He had lost approximately 20 pounds during the previous 2 months. He gave a history of rheumatic fever associated with ulcers of the rectum and frequent loose, bloody stools 6 years prior to entry.

On admission the temperature was 100.2°F., the pulse 94, the respirations 22, and the blood pressure 120/80. The patient appeared to be fairly well nourished and of normal development. There was slight generalized abdominal spasm. On rectal examination there was marked spasm of the sphincter and there was blood on the examining glove, but no masses or ulcers were palpated. The remainder of the physical examination was negative.

The patient was treated on the medical service for 23 days without success. During that time the temperature fluctuated between 99 and 103°F. and the diarrhea became severer. While the patient was on this service, large punched-out ulcers on the rectal wall were demonstrated by sigmoidoscopy on two occasions. Two barium enemas were interpreted as showing marked spasm of the sigmoid, with diminished haustral markings and multiple irregularities of the transverse and sigmoid colon. In addition, there was a constant filling defect of the cecum.

On the 23rd hospital day, the patient was transferred to the Fifth Surgical Service for ileostomy. This was performed under spinal anesthesia on the day of transfer. At operation, the cecum and colon were found to be thickened and hyperemic. The external appearance of the terminal ileum was not noteworthy. A loop ileostomy was performed approximately 7 cm. proximal to the ileocecal valve. The patient withstood the operation well. During the next 5 days he continued to have diarrhea and began to suffer from crampy abdominal pains and vomiting. On the 5th postoperative day, the loop of the ileum was opened. Vomiting continued and the blood chlorides became depleted. This was corrected by administering intravenously large amounts of normal saline solution. The vomiting gradually decreased and the temperature gradually returned to normal, so that by the 34th postoperative day it was believed that the patient was definitely improved; however, the ileostomy discharge continued to be loose and the patient had occasional bloody movements by rectum.

On the 56th postoperative day, the patient again began to suffer from severe abdominal cramps and vomiting. His condition became progressively worse, and he died on the 60th postoperative day.

Laboratory studies during the hospital stay showed the red-cell count to be 3,000,000 and the hemoglobin 60 per

cent. The white-cell count varied between 10,100 and 16,700, with 70 per cent neutrophils, 17 per cent lymphocytes, 2 per cent monocytes and 1 per cent basophils. The cell morphology was not remarkable. Repeated urinalyses showed traces of albumin and many white cells and two specimens contained red cells. A blood Kahn test was negative. The skin reactions to 1:10,000, 1:100,000 and 1:1,000,000 dilutions of tuberculin were negative. Agglutination tests against typhoid, paratyphoid and *Brucella* organisms were negative. Two blood cultures showed no growth. Stools were always guaiac positive, and microscopic examination revealed no ova or parasites. Repeated cultures of stools were negative for pathogenic organisms. A biopsy of a rectal ulcer showed chronic inflammation.

Autopsy (35-202). At autopsy the body was that of a poorly nourished man. In the right lower quadrant, level of the anterosuperior spine of the ileum, were two openings in the anterior abdominal wall, each 3 cm. in diameter and each containing an open end of ileum. Through the peritoneal cavity 800 cc. of thick, bright red, foul-smelling, purulent matter was found. Many loops of small intestine were matted together by fibrin, and in addition, other loops of small bowel were adherent to the ascending and descending colon and to the bladder and rectum. The small intestine was moderately distended. Ten to fifteen centimeters above the ileocecal valve and 15 cm. from the ileostomy wounds were two round perforations in the wall of the ileum, each approximately 1 cm. in diameter. Beginning at a point 60 cm. above the ileocecal valve, extending throughout the entire colon and rectum, there was a marked ulceration of the mucosa of the bowel. The ulcers varied in size, were clearly defined and irregular in shape, and had ragged, gray-black bases. In many areas the ulceration had been undermined, leaving bands of mucosa with attachment to underlying tissue. In some areas the ulcers were confluent so that the bowel wall was denuded for a distance of 7 to 10 cm. The ulceration appeared of equal severity throughout the colon, but at the site of perforation in the ileum it was especially severe.

Sections of the ileum showed the serosa to be covered by an exudate consisting chiefly of fibrin and polymorphonuclear leukocytes. The mucosa was ulcerated and this process extended into the muscularis. The submucosa and the muscularis were diffusely infiltrated by plasma cells and lymphocytes. Sections of the colon showed extensive ulceration of the mucosa and muscularis, with infiltration by plasma-cell and lymphocytic infiltration.

Cultures of ulcers in the ileum and from the peritoneal cavity showed *Escherichia coli*, alpha-hemolytic and non-hemolytic streptococci and *Proteus vulgaris*. Type 8 *Staphylococcus aureus* was cultured from the heart's blood.

In addition to the lesions described, the patient was found to have bronchopneumonia of both lower lobes and pulmonary congestion and edema.

The anatomic diagnoses were ulcerative colitis, ulcerative ileitis with perforation, generalized peritonitis, bacterial pneumonia, and pulmonary congestion and edema.

CASE 2. H. S. (B.C.H. 987,922), a 44-year-old, white woman, was admitted to the medical service on June 1, 1940, complaining of bloody diarrhea of 10 months' duration. She stated that she had had from fifteen to twenty bloody stools every twenty-four hours, and that the stools had contained bright red blood and occasionally mucus. In addition, she suffered from crampy pains in the umbilical region. She estimated that she had lost 20 pounds in weight during the course of her illness.

Physical examination on admission revealed a moderately developed, poorly nourished, excitable woman who gave the appearance of being chronically ill. The temperature 100°F., the pulse 100, the respirations 16, and the blood pressure 125/85. The left cardiac area was perforated. There was a short systolic precordial murmur. There was no ulceration of the cervix.

The patient was placed on a high-vitamin, low-calorie diet, supplemented by various vitamin preparations, including bismuth subcarbonate and belladonna. There was a moderate decrease in the diarrhea. Proctoscopy showed multiple undermined ulcer craters with dirty-gray bases which bled easily. Scrapings from the craters were negative for amebae. The patient was given sulfathiazole, with some improvement, and because she developed toxic symptoms this drug was discontinued. Since all efforts to control

diarrhea were unsuccessful and the patient was obviously failing, she was transferred to the Fifth Surgical Service on the 59th day for ileostomy. At the time of transfer there was a foul, purulent vaginal discharge from a rectovaginal fistula.

Ileostomy was performed on the day of transfer under intravenous Pentothal Sodium anesthesia. The terminal ileum was divided 15 cm. from the ileocecal valve, and the distal end was brought through a separate stab wound in the McBurney area. At that time the serosal surface of the terminal ileum appeared normal.

The patient's postoperative condition was poor. The temperature was 102.4°F., the pulse 120, and the respirations 22. There was a persistent, profuse discharge from the ileostomy wound. Large quantities of normal saline solution were administered intravenously, and fourteen blood transfusions were given in an effort to maintain the total serum protein and hemoglobin, which averaged 4.5 gm. and 65 per cent, respectively.

Two weeks postoperatively, the patient developed severe, cramplike abdominal pains and began to vomit. The ileostomy drainage temporarily ceased. She was placed on Wangersten drainage and responded well, so that in 2 days all signs of obstruction had disappeared. Starting with the 4th postoperative week, her appetite became progressively poorer and it was necessary at times to resort to forcible feeding through an inflying Levine tube. Large doses of thiamine chloride and ascorbic acid were given daily.

During the 6th postoperative week, the patient developed signs of acute pericarditis, and this diagnosis was confirmed by x-ray. Purulent material was obtained on aspiration of the pericardium, and on culture *aureus*, fusiform bacilli and tained. Pericardiostomy was patient remained in shock for five treatment, which included blood. At that time she also developed a panophthalmitis of the right eye. During the following 6 days the patient recovered from shock. The pericardial cavity was irrigated regularly. On the afternoon of the 6th day following pericardiostomy, the 49th day following ileostomy, she suddenly complained of pain in the right lower quadrant of the abdomen. Examination of this area showed tenderness and spasm. The pulse and respirations rose rapidly, the patient's condition generally deteriorated, and she died 12 hours later.

Autopsy (40-828). At autopsy the body was that of an emaciated woman. There was a recent open operative wound over the heart measuring 11 by 4 cm. Portions of the 5th and 6th ribs had been removed, leaving a window 4 by 4 cm., opening directly into the pericardial cavity. There was a well-healed scar of the right rectus muscle, as well as a healed ileostomy scar on the right. There was a patent ileostomy in the midline. When the peritoneal cavity was examined, the omentum was adherent to the ileum at a point 6 cm. above the ileostomy wound. A small perforation was found in the wall of the ileum at that point, and the serosal surfaces were covered with thick, fibropurulent exudate. There was 300 cc. of cloudy fluid flecked with fibrin in the lower abdomen and pelvis. *Staph. aureus* and alpha-hemolytic streptococci were cultured from this fluid. There were no further ad-

hesions, either old or recent, in the peritoneal cavity. The distal stump of the ileostomy was well healed and was 8 cm. above the ileocecal valve.

The esophagus, stomach, duodenum, jejunum and proximal portion of the ileum were normal. Beginning at a point 15 cm. above the ileostomy were a series of approximately fifteen small ulcerated areas in the mucosa. These mucosal lesions had an irregular, punched-out appearance, and each measured approximately 4 mm. in circumference. There were a few dense white scars that apparently represented healed ulcers. One of the active ulcers had perforated as described above. The ileum distal to the ileostomy contained feces.

areas from which mucosa at the edge of the ulcers and the muscularis underlying the base of the ulcer were infiltrated by lymphocytes and plasma cells.

Ulcerations were found in the ascending colon and rectum. The ulcers in the rectum were large and tended to coalesce so that large areas were denuded of mucosa, leaving the muscularis bare. Sections showed necrosis and sloughing of the mucosa. There was marked infiltration of the remaining mucosa by lymphocytes and plasma cells. These lesions were much severer than those seen in the ileum. *E. coli* and *Pseudomonas aeruginosa* were cultured from these ulcers. The rectum and vagina were adherent in places, and there were two small fistulas between these organs.

The epicardial and parietal pericardial surfaces were smooth or gross adhesions or gross thickening of the pericardial tissue, together and a few bacteria.

In addition to the above lesions there was moderate atelectasis and a slight amount of bronchopneumonia in the right lower lobe.

The anatomical diagnoses were ulcerative colitis, ulcerative ileitis with perforation, peritonitis, purulent pericarditis (healing), pyohemothorax (left), atelectasis (left lower lobe), bronchopneumonia (left lower lobe) and rectovaginal fistulas.

SUMMARY

Two cases are described in which perforation of the ileum above the site of ileostomy with resulting peritonitis occurred following operation.

It is suggested that, in cases of prolonged severe ulcerative colitis, ileostomy, if indicated, be performed at least 90 cm. above the ileocecal valve.

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heart, arrhythmias and electrocardiographic abnormalities, constitute a clinical picture that may appear indistinguishable from that of acute myocardial infarction. In order to make the correct diagnosis it is necessary to realize that the two conditions may resemble each other closely and then to consider certain of the features in detail. The differential diagnosis may be difficult. In 4 of the 5 cases described above a diagnosis of cardiac infarction was at first actually made or seriously considered, and in 3 of these 4 cases it was possible to discard the diagnosis of infarction only after careful observation. The following points have been found useful in differentiating acute pericarditis from acute myocardial infarction.

Pain. The distinguishing feature is accentuation of the pain by bodily movements, cough and inspiration. It is important to elicit the fact that characteristically the aggravation of the pain on exertion is not due to effort but to certain movements, such as turning over in bed. The aggravation of the pain by motion, cough and inspiration is present from the very outset in pericarditis, whereas when it occurs in myocardial infarction it is usually first noted twenty-four or forty-eight hours or more after the onset of the pain, and probably indicates that the infarct has extended to the pericardium or that some complication has arisen.

Dyspnea. Although dyspnea may be associated with pulmonary congestion, in most cases it can be ascertained that it is consequent to rapid, shallow breathing due to pain that interferes with the respiratory movements.

Pericardial friction rub. In most cases of myocardial infarction a friction rub is never heard; when present, it is rarely heard in the first twenty-four hours, is usually localized, and lasts only a short time. In acute pericarditis, on the other hand, the rub is heard within one to a few hours after the onset of pain, tends to be very loud, is audible over the entire precordial area, and is constantly present for days or for even one or two weeks.

Pleural involvement. Pleural involvement was demonstrated in 4 of the 5 cases of pericarditis by the presence of a pleural friction rub or by thickening of the pleura and a small collection of pleural fluid on x-ray examination. The fifth patient was not studied by x-ray.

Cardiac dilatation. The heart dilates in some cases of acute pericarditis² to a degree that exceeds that seen in myocardial infarction; nevertheless, myocardial failure does not occur in acute pericarditis. The only reliable method of detecting acute dilatation in these cases is teleroentgenography.

Abnormal ventricular pulsations. In 75 per cent of the cases of myocardial infarction a localized area of diminished, absent or reversed ventricular pulsations is found on careful fluoroscopic observation.³⁻⁷ No such abnormalities of ventricular pulsation were demonstrable in these cases of pericarditis.

Electrocardiograms. Characteristic electrocardiographic patterns occur in acute pericarditis and acute myocardial infarction; they are readily differentiated in spite of certain similarities. The pattern in acute pericarditis is sufficiently distinctive to permit the diagnosis to be made even in the absence of a pericardial friction rub. Elevation of the RS-T segment is not accompanied by reciprocal depressions, the ascending limb of the T wave is straight or concave upward or the T wave is dome-shaped, significant QRS patterns do not occur, and the evolution of the entire pattern with reversion to normal takes place in a matter of weeks.¹ To avoid overlooking the pattern of infarction, however, an electrocardiogram should be obtained as early as possible, and be frequently repeated until the diagnosis is established beyond any doubt. Multiple chest leads should be used.

Fever. When temperature elevation occurs in pericarditis, it may be noted at the very onset of the attack. It may reach a higher level and last much longer than is usual in cases of acute myocardial infarction.

Pulse rate. The slowness of the heart rate may be striking in pericarditis; the average heart rate is slower than it is in cases of myocardial infarction.

White-cell count. Leukocytosis may be much greater and may last much longer in pericarditis than in infarction.

Age incidence. The ages of the above patients with pericarditis were thirty, twenty-nine, thirty-two, forty-one and sixty-eight years, respectively, a lower average than one would expect in myocardial infarction.

Manifestations of infection. Chilliness, chills, a "grippy" feeling and actual respiratory infection were more numerous in this series than they are in cases of infarction.

DISCUSSION

The importance of not mistaking acute pericarditis for acute myocardial infarction needs little comment. The serious prognosis in the latter disease, the long period of incapacity and the frequent necessity of radically altering the patient's life contrast strikingly with the excellent prognosis and the expectancy of unrestricted activity in the former. In the one disorder there is always present the anxiety of some untoward event; in the other one can look into the future with confidence, even though recurrences of pericarditis occur in some cases.²

This problem in differential diagnosis has not been generally appreciated because of the belief that pericarditis usually or always occurs in association with rheumatic fever, tuberculosis, pneumonia, septic infections and cardiac infarction. The evidence warrants the assertion that in the cases here reported rheumatic fever, tuberculosis, septic infection and myocardial infarction can be excluded as etiologic factors. In Case 1 pericarditis complicated recovery

from primary atypical pneumonia; in Cases 2 and 3 it appeared without any previous illness or symptoms of infection, although pharyngeal injection was found in Case 2, and in Case 5 it occurred in an elderly man with chronic bronchial asthma. An unusual aspect in Case 4 was the coincidental presence of angina pectoris.

It is probable that the pericarditis in the cases here described was infectious in origin, although not of uniform etiology. With the onset of pericarditis in Case 4, manifestations of infection — that is, a "grippy" feeling, chill, a high white-cell count and marked febrile reaction — were prominent. Four or five attacks of pericarditis occurred during a seven-month period, illustrating, as did Case 2, the predisposition to recurrences. A benign, nonsuppurative, inflammatory pericarditis may apparently occur under various circumstances, unassociated with the commonly recognized causative factors. It may follow tonsillectomy. It has been reported following operative procedures^{8,9} and has been observed in epidemic form.¹⁰ Occurring as a postoperative complication and associated with a grayish pallor, a rapid, weak pulse and a drop in blood pressure, it may be erroneously diagnosed as pulmonary embolism or myocardial infarction.⁹

Barnes and Burchell¹ express the opinion that the correct diagnosis depends chiefly on the correct interpretation of the electrocardiographic changes, which they describe in detail. They do, however, consider the age incidence, the relation of the pain to inspiration and the marked cardiac dilatation as helpful in making the correct diagnosis. These, as

well as the other manifestations discussed above, should establish the diagnosis on a firm basis.

SUMMARY

Five cases of acute nonsuppurative pericarditis are reported in which the clinical picture strikingly simulated that of acute myocardial infarction. The latter diagnosis was at first erroneously made in 4 of them.

It is important to make the correct diagnosis, since in pericarditis prolonged and careful treatment is not necessary and the prognosis is excellent, in contrast with the seriousness of myocardial infarction.

The differential diagnosis is discussed and shown to be based on meticulous consideration of clinical, laboratory, electrocardiographic, teleroentgenographic and fluoroscopic data.

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MEDICAL PROGRESS

DIABETES MELLITUS

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ALLOXAN DIABETES

THERE are now three methods by which diabetes can be caused experimentally: the removal of the pancreas, discovered by von Mering and Minckowski; repeated injections of anterior pituitary extract, finally accomplished by Young but based on the work of Houssay, Evans and others; and the injection of a chemical — namely, alloxan. In the April 17, 1943, issue of the *Lancet*, Dunn, Sheehan and McLetchie¹ in Glasgow described how they had produced a selective necrosis of the islets of Langerhans of the pancreas in rabbits by injection with alloxan. Within a few weeks this paper was followed by others from groups from Chicago, Boston and

Glasgow, in which it was shown, as might be expected, that if the animals were kept alive, diabetes developed as a result of the necrosis of the islet tissue.

Chemically alloxan is the uride of mesoxalic acid, and as a result of its four carbonyl groups it is chemically a very active substance. Structurally it is closely related to the purines, particularly to uric acid. It may act either as a strong reducing agent or as an oxidizing agent. Its activity as an oxidizing agent is probably directly related to its ability to act as a hydrogen acceptor. As a hydrogen acceptor its affinity for the sulphydryl groups may be of particular biologic significance.² Lehmann³ found that alloxan inhibits the conversion of the Cori ester to the Robison ester and in higher concentrations the formation of the Cori ester itself.

Alloxan is readily soluble in water, forming a slightly acid solution. It is relatively stable only in acid solution. Labes and Freisburger⁴ suggest that the mild alkalinity of the blood and tissues is probably sufficient to cause decomposition of any free alloxan almost immediately unless it enters into some other reaction. Through reduction it becomes alloxantin, whereas through oxidation it changes to parabanic acid.

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Alloxan is easily obtained from the oxidation of uric acid with nitric acid. Its relation to the role of uric acid in the body is, therefore, of possible significance. Uric acid in the human body originates exogenously in nucleoprotein in the food and therefore varies in amount according to the diet, but also originates endogenously. Uric acid eliminated in human urine amounts to 0.4 to 1.0 gm. daily, as compared with 20 to 35 gm. of the more highly oxidized urea. The excretion of uric acid is known to increase with muscle exercise. Muscle is not only the greatest consumer of sugar but is also the chief source of endogenous uric acid.

The deep significance of the production of diabetes by a chemical lies first in the simplicity and sureness of the method. Previous methods required technical skill or considerable time and labor. Furthermore, by pancreatectomy or by injections of mixed anterior pituitary extracts, other tissues than the insulin-producing islands were involved. Moreover, the use of the rabbit and rat affords animals easily available and suitable for research, thus opening up avenues for investigation of diabetes that were previously unavailable. The importance of the discovery merits a more detailed summary of these studies.*

In 1937, Jacobs⁴ found that alloxan produced fatal hypoglycemia when injected intravenously into rabbits. Microscopic studies of the pancreas were not made. Recently in studies on the crush syndrome and mismatched blood transfusions Dunn experimented with injections of uric acid, which he had previously observed caused a selective lesion in the distal convoluted tubules and collecting tubules and other allied substances. He noted that alloxan gave promising results but that the animals died within the first day or so with symptoms not referable to renal disease, and it was in the course of these investigations that a lesion was found in the islands of Langerhans.

In a protocol of one of the rabbits three doses of alloxan were given intravenously in half an hour, each dose amounting to 100 mg. per kilogram of body weight in a 2 per cent solution of distilled water. The next morning the rabbit was in a feeble state, and later it was comatose, with slow, feeble breathing. The rectal temperature, normally 102 to 103°F., was below 93°F. The animal was chloroformed and an autopsy performed twenty-eight hours after the beginning of the experiment; the blood urea was 101 mg. per 100 cc., but the blood sugar was only 59 mg. compared with a normal of 100 to 140 mg. The kidneys showed an early tubular nephritis. No changes in other organs were noted save in the pancreas. Dunn, Sheehan and McLetchie describe these as follows:

The acinar tissue appeared normal; some eosinophil casts were present in ducts. The islets of Langerhans were all

abnormal; in most of them there was complete necrosis of the central cells, leaving only a ring or a crescent of live cells at the periphery; rarely, all the endocrine cells were necrotic. The protoplasm of the dead cells had the characteristic appearance of coagulative necrosis and often their bodies had fused into a mass. The nuclei had lost all the normal basophil staining of chromatin and took on eosin more intensely than did the protoplasm; their edges were ill defined as if they were undergoing lysis. The surviving peripheral cells generally had nuclei of normal appearance, as had sometimes their protoplasm, but very often the cell bodies were somewhat swollen and definitely eosinophilic though evidently not necrosed; in some of these the nuclei were small and hyperchromatic.

In subsequent experiments death occurred in twelve to twenty-eight hours following the injection, save in one rabbit that was killed in forty-eight hours and another that was killed on the fifth day. All the rabbits injected with alloxan showed some degree of islet necrosis. The authors concluded that a single intravenous dose of 300 mg. per kilogram of body weight given to an adult rabbit of average nutrition could be depended on to produce an extensive lesion of the islands, with characteristic symptoms. The blood sugar, initially 100 to 140 mg. per 100 cc., rose considerably for the first one or two hours, reaching 380 mg. in one case, and then fell in three to five hours to 100, 50 or even 30 mg. The terminal phase may not always have been seen, the animal having been killed to ascertain the state of the pancreas. No glycosuria was detected in any of these animals.

These authors summarize their work in part as follows:

Acute necrosis of almost all the islet tissue of the pancreas has been observed in rabbits after intraperitoneal inoculation of a synthetic styryl-quinoline, and also after intravenous inoculation of alloxan. The development of this lesion is accompanied by an initial rise of blood sugar, followed by an intense hypoglycemia which ends fatally with subnormal temperature in twelve to eighteen hours. It is suggested that the lesion may be caused by overstimulation of the islets with overproduction of insulin, and later death of the cells from overstrain. The mechanism of production of the lesion is discussed and reference is made to the possible role of alloxan as a hormone of muscle.

* * *

In a letter to the editor of the *Journal of the American Medical Association*, Brunswick, Allen, Goldner and Gomori⁵ confirmed the work of the Glasgow observers and also stated that they had observed animals that survived injections of alloxan and exhibited only transitory hyperglycemia. They found that alloxan in doses of 200 to 500 mg. per kilogram of body weight was fatal to dogs in one hour to five days. They also noted that the transitory hyperglycemia was followed by hypoglycemia and by the end of forty-eight hours a pronounced hyperglycemia again occurred, which persisted in five dogs for two or three weeks. They also injected alloxan into 3 patients with carcinomatosis, apparently without much effect. In a subsequent communication, however, these cases and 2 others, in one of which the patient had an insulin-producing pancreatic carcinoma, were studied in detail by Brunswick, Allen, Owens and Thornton,⁶ who confirmed the earlier work in showing little influence of alloxan on the first 3 cases of noninsulin-producing cancer.

*Brief mention should be made of another chemical, styryl-quinoline No. 90, of which the full name is 2 (p-acetyl-amino-styryl) 6-dimethyl-amino-quinoline methochloride. According to Dunn, Sheehan and McLetchie, this substance, prepared by Cohen and Ellingworth, when tested by Brown and Gulbransen was found to have curative properties for infections with *Trypanosoma brucei*, but was inapplicable because it sometimes caused acute nephritis. In a subsequent study of this nephritis in rabbits, Sheehan observed that the animals lay prone with the hind legs stretched and the head tilted upward, with rapid respirations. The blood examination revealed a rise of blood sugar as high as 500 mg. per 100 cc. and the animals died in twelve to eighteen hours. Histologic examination showed a necrosis of the islands of Langerhans. No distinctive lesions were found in any other organs save the kidneys.

The alloxan did show a distinct reduction in the hypoglycemic attacks of the patient with the malignant tumor of the islet cells. The patient had had marked attacks, dating as far back as 1937, and had undergone operations for these by removal of islet-cell nodules from the pancreas or liver in September, 1939, in January, 1940, in August, 1942, and finally in December, 1943. Temporary symptomatic relief of these attacks was obtained, since the attacks were obliterated for a brief period following each series of injections. Shortly after the last laparotomy, the patient succumbed to an accidental complication. Autopsy revealed multiple metastatic nodules within the liver. Sections of the surgically removed pancreas showed normal acinar tissue and no evidence of necrotic islet cells. Sections of the tumor nodules showed viable tumor cells and no evidence of necrosis comparable with that seen in the islet cells in the pancreases of dogs and rabbits receiving alloxan. There was no evidence of acute damage to the liver cells, and no necrosis of the epithelium of the convoluted tubules.

Two other features of this case deserve mention. First, as a result of repeated attacks of hyperinsulinism, a tolerance for low blood-sugar levels had developed and the patient was able to conduct himself normally with a level as low as 20 mg. per 100 cc., the attack level being 14 mg. or less. Second, forced ingestion of food in an attempt to ward off hypoglycemic attacks resulted in a 35-pound gain in weight over a period of seven months after the carcinomatosis of the liver was proved by laparotomy, thus suggesting, as the authors state, that the cachexia of carcinoma is merely the result of a gradual reduction of the caloric intake and not of a toxemia originating from tumor cells.

The fifth patient was given the largest single injection of alloxan of the entire group, and died six hours after termination of the injection. This patient had a large carcinoma of the lower rectum, which had been previously excised. The patient returned with various complications, and reacted with few symptoms on August 27, 1943, when he was given 200 mg. of alloxan per kilogram of body weight, dissolved in 1000 cc. of an isotonic solution of sodium chloride. On September 1, however, when he received 600 mg. per kilogram of body weight, dissolved in 1200 cc. of saline solution, he developed a moderately severe chill and cyanosis and some six hours later, having apparently recovered from the symptoms following the injection of alloxan, suddenly died.

* * *

If alloxan produces extensive necrosis of the islands of Langerhans without damage to its acinar tissue and relatively minor changes in other organs, so argued Bailey and Bailey,⁷ it would be reasonable to suspect that the hypoglycemic phase following the injection of the drug is transitory. Should this

prove to be true, animals kept alive by repeated injections of dextrose might survive this hypoglycemic phase and finally develop diabetes mellitus. A series of experiments designed to test this hypothesis showed that such is the case.

Three-month-old male Dutch rabbits were employed. Each received intravenously 200 mg. of alloxan per kilogram of body weight, the injection being given in three parts over a period of forty-five minutes. The rabbits were observed continuously for sixteen to twenty-four hours, and 50 per cent glucose was given intravenously whenever hypoglycemic convulsions occurred. These authors also found an initial transitory hyperglycemia lasting approximately one hour after the injection of alloxan, followed by severe hypoglycemia with convulsions, but in less than twenty-four hours the hypoglycemic stage ended, leaving the animals with severe diabetes. Blood-sugar levels during the diabetic state ranged from 360 to 700 mg. per 100 cc. and glycosuria up to 10 per cent. One rabbit not given insulin developed acetonuria, total acetone bodies of 144 mg. per 100 cc. and pronounced lipemia, with total blood lipids of 8412 mg. per 100 cc. Insulin, $1\frac{1}{2}$ to 8 units daily, was given to control the diabetes.

Two rabbits were killed, and it was found that the cells, both alpha and beta, of all the islands of Langerhans had completely disappeared. No polymorphonuclear infiltration was seen. The blood vessels of the islands were preserved and appeared entirely normal. Some of the pancreatic ducts were moderately distended and contained eosinophilic material. Their epithelium, as well as that of all the acini, showed no changes detectable on microscopic examination.

The following is a representative experiment in the series:

Rabbit 1, weighing 1520 gm., was entirely normal during a 7-day period of observation. Food was withheld for 18 hours, at the end of which time blood sugar determinations were 105 and 110 mg. per 100 cc. (100 and 110 hundred and four milligrams of glucose per 100 m of body weight) was then injected intravenously in three divided doses at 15-minute intervals. Fifteen minutes after the end of the last injection the blood sugar was 208 mg. per 100 cc. An hour later it was 105 mg., and 2½ hours after the end of the injection it was 38 mg. The first convulsion developed 10 minutes later. Prompt recovery followed the administration of 2 cc. of 50 per cent dextrose intravenously. In the next 13 hours eleven more hypoglycemic convulsions occurred, each relieved promptly by dextrose intravenously. On the morning after the injection of alloxan the blood sugar was 190 mg. per 100 cc. and rose to 640 mg. on the 3rd day. The rabbit was kept in good condition for sixteen days, during which time the blood sugar was constantly increased, and the body weight increased to 540 mg. Persistent glycosuria accompanied the hyperglycemia, the daily dextrose excretion varying between 10 and 22 gm. Definite polydipsia and polyuria were observed, with the water intake ranging between 350 and 700 cc. and urinary excretion between 160 and 470 cc. daily. The body temperature was 104°F. before the experiment was begun and fell to 99°F. at the end of 11 hours, but subsequently returned to normal.

Repeated urinalyses failed to show albuminuria or any abnormal sediments. The blood nonprotein nitrogen varied from 36.3 to 65.0 mg. per 100 cc., whereas normal controls taken prior to the experiments ranged from 42.6 to 60.0 mg.

Bailey and Bailey consider that the initial blood sugar rise may be similar to a transitory hyperglycemia produced in rabbits by the injection of a number of substances and therefore not of great significance.

The cause of the prolonged yet limited period — twelve to twenty-four hours — of hypoglycemia that follows the injection of alloxan is at the present time debatable. Dunn, Sheehan and McLetchie¹ suggest that it may result from a primary stimulation of the islet cells. Another possible explanation is that necrosis of the islets releases a large amount of insulin.

* * *

In a second article, Dunn, Kirkpatrick, McLetchie and Telfer⁸ point out that selective necrosis of the islands of Langerhans in the pancreas has rarely been described in human beings. They cite Pettavel,⁹ who in 1912 and again in 1914 observed it in a case of hyperthyroidism associated with alimentary glycosuria. Fischer¹⁰ in 1915 noted necrosis in a child of six and a half years with severe and rapidly fatal diabetes, and cites Heiberg¹¹ as considering this lesion to represent the commencing defect that is commonly noted in diabetes. Dunn et al. reaffirmed their previous findings of necrosis in the islands of Langerhans in rabbits injected with alloxan. The acinar tissue of the pancreas remained in all cases histologically normal, even at the edge of totally necrosed islets. They cite only negligible changes as having been observed in the adrenal, thymus, thyroid and pituitary glands. In the kidneys the changes were fairly extensive, with necrosis of the proximal and sometimes of the distal convoluted tubules. The renal lesions they considered as probably due to concentration of the toxic agent in the tubules during the process of excretion, but whether this was caused by alloxan or a degradation product of the same was unknown. At times renal changes were minimal when the islet lesion was fully developed.

Fatal doses of alloxan in rabbits usually varied between 200 and 300 mg. per kilogram of body weight, the injections sometimes being divided over periods of a half to six hours. Three hundred milligrams invariably caused necrosis of the islands, although some animals survived.

Styryl-quinoline No. 90 is the only other chemical known to cause islet necrosis. The authors tried the effect of oxalic acid, uranium, guanidine and uric acid, with no comparable lesions resulting. They also tried glucose in solutions as strong as 25 per cent.

Alloxan produced similar lesions in rats and mice. Permanent glycosuria and many features of the diabetic state were recognized in 5 of 8 albino rats injected. The glycosuria could be controlled by insulin.

Death of the islet cells is the chief factor following injection of alloxan. No island remains unscathed, and in some islands apparently no cells survive.

Any living cells are at the periphery, where they may share the blood supply of acinar tissue.

* * *

Subsequently Dunn and McLetchie¹² recorded their investigation of alloxan diabetes in the rat. With doses of 300 to 400 mg. per kilogram of body weight some acute damage of the islands of Langerhans was produced, occasionally with necrosis in the renal tubules. Glycosuria was observed with almost all the symptoms of diabetes in certain of the rats, although 1 rat appeared to be recovering after two months. The glycosuria was controllable with insulin. In these rats the protoplasm of the islets was eosinophilic and hyaline, with pyknotic nuclei. In two islands there was a peripheral layer of large cells free from necrosis, which the authors thought were alpha cells, the beta cells being the cells chiefly affected. Mitoses were rare. They describe an acute effect of alloxan as follows:

No. 11 died, cold and drowsy, at 48 hours; there was no glycosuria. The changes in the islets were as in No. 9 but more severe, with more necrotic debris and more cells of doubtful viability; while obviously live cells were fewer. There were, in addition, very pronounced lesions in the small ducts in this pancreas, comprising dilatation and accumulation of wax-like eosinophil masses with leucocyte infiltration in the walls and in the interstitial septa; this lesion could be interpreted as an early pancreatitis.

They also noted that the general appearance of the islands suggested reparative changes, but they saw "none of the more characteristic islet changes described in the human disease — sclerosis or hyalinisation of islets or hydropic changes in their cells."

* * *

An intraperitoneal injection of 200 mg. of alloxan per kilogram of body weight was found to be almost invariably effective in producing diabetes by Gomori and Goldner¹³ when given to 40 rats. Of the 27 animals studied in detail, only 4 were resistant to alloxan. All the others showed hyperglycemia and glycosuria. Ketonuria was observed from the third day on and was present on subsequent days in all animals that had a blood sugar level above 300 mg. Some of the animals had a pink urine on the first day after the injection. In rats killed at the end of twenty hours, an overwhelming majority of the beta cells were greatly shrunken. In some cases the cell cords either had disintegrated into individual cells or had coalesced into an almost homogeneous debris. On the second day these changes were more accentuated, and the beta cells had started to lose the typical staining of their granules. On the fourth and fifth days only an occasional beta cell could be seen. At the same time, agranular cells of an unidentifiable type appeared in large numbers and filled the areas previously occupied by the necrotic beta cells. At the periphery, the alpha cells had proliferated considerably. By the fifth and sixth days the islets were entirely free from debris and with the routine hematoxylin-eosin stain looked practically normal.

Special stains, however, showed that they consisted of agranular and alpha cells only, beta cells being completely absent. No vacuolation of the islet cells was recognized at any stage. Mitoses were extremely rare, and the acinar parenchyma showed no change. The liver contained very little glycogen after the second day but was otherwise normal, except in 2 animals in which focal necroses were observed. The kidneys showed nothing of importance except that, from the fourth day on, deposition of glycogen in Henle's loops was quite frequently observed.

Five "hooded rats" were resistant to alloxan, possibly owing, as the authors suggest, to the exceptionally large amount of islet tissue that this strain possesses.

The histologic changes of the pancreas obtained by a single intraperitoneal injection appeared similar to those obtained by Dunn, Sheehan and McLetchie¹ with repeated subcutaneous injections of alloxan.

* * *

Goldner and Gomori¹⁴ have extended their observations on alloxan diabetes in dogs. According to the dosage of alloxan administered varying changes occurred, and they divide their experiments into four groups.

Group 1. Alloxan, above 100 mg. per kilogram. Dogs receiving this dosage died within eight hours in sudden convulsive attacks. Microscopic examination showed no changes in the islands. Although in one animal the glycosuria fell to 48 mg., death was not attributed either to hypoglycemia or to kidney damage.

Group 2. Alloxan, 75 to 100 mg. per kilogram. These animals were hypoglycemic, then hyperglycemic, and presented what the experimenters considered to be a uremic syndrome. They died in four to seven days, gradually becoming drowsy and then semicomatose, without convulsions but developing oliguria and eventually anuria. The hyperglycemia in 1 case reached 800 mg. per 100 cc. There was also a steady rise in nonprotein nitrogen, attaining in 1 case 275 mg. per 100 cc. In only 1 case was albuminuria noted. No ketonuria was found. Microscopically the absence of granules in the beta cells was apparent, but the alpha cells were unchanged. There was no vacuolation in the cells of the islands or ducts. Extensive necrosis of the convoluted tubules was apparent, with glycogen in Henle's loops. The liver was normal.

Group 3. Alloxan, 50 to 75 mg. per kilogram. Dogs receiving this dosage developed diabetic symptoms and signs — polydipsia, polyuria, loss of weight, hyperglycemia and glycosuria. There was no ketonuria, albuminuria or increase in nonprotein nitrogen, but there was an increase in lipemia and the respiratory quotient fell to about 65. Pathological examination revealed small islands, no normal beta cells and no hydropic degeneration of the beta cells. There were no mitoses of the islet cells. Extreme vacuolation of the epithelium of all intralobular ducts occurred in the later stages of the disease. The kidneys were normal save for the presence of glycogen. There was fatty infiltration of the liver, with 31 per cent lipids, and the phosphatase reaction was increased.

Group 4. Alloxan, 25 mg. per kilogram. This dose was ineffective.

In summary, intravenous administration of alloxan to dogs in a single dose exceeding 100 mg. per kilogram of body weight caused death of the animals within a few hours. A dose of between 75 and 100 mg. produced a diabetic uremic syndrome of which the animals died within a week. A dose of 50 to 75 mg. produced typical diabetes without renal lesions, and these animals were kept alive for weeks. The

main histologic features were a disappearance of beta cells from the islets, profound vacuolation of the epithelium of the pancreatic duct and fatty changes of the liver. Doses of 25 mg. were without effect.

* * *

In studies on the insulin tolerance, Dragstedt, Allen and Smith¹⁵ observed that more insulin appeared to be required to establish the control of glycosuria in dogs with certain types of partial pancreatectomy than in totally depancreatized dogs. Likewise, in 2 dogs made diabetic by the intravenous injection of alloxan, the requirement of insulin was 32 and 36 units of regular insulin daily, which Goldner and Gomori consider somewhat greater than that for depancreatized animals at the same period.

* * *

In their second article, entitled "Alloxan Diabetes with Diabetic Complications," Bailey and Bailey¹⁶ have advanced materially the knowledge of the action of alloxan in rabbits and rats and have shown clearly how closely the disease in the experimental animal approaches that in human subjects. They report that cataracts were found in all such rabbits within four to six weeks after the diabetes was induced. These were chiefly subcapsular and were more advanced in the posterior cortex, where they appeared earlier than in the anterior cortex of the lens. Like previous workers, these authors found the histologic changes in the animals to be confined to the islands of Langerhans, save for mild tubular degeneration of the kidneys and slight fatty metamorphosis of the liver.

A gradual onset of diabetes, thus more closely resembling the usual variety found in human beings, was obtained by the Baileys when alloxan in doses of 40 mg. per kilogram of body weight was given to rabbits in repeated intravenous injections. In 2 such rabbits after the seventh and the thirteenth injection, respectively, the blood sugars were over 200 mg. per 100 cc. and were accompanied by glycosuria, and the islet cells showed a variety of lesions, described as follows:

Some cells, especially those at the periphery of the islets, appeared essentially normal. In other cells, the nuclei were well preserved, as was the ground substance of the cytoplasm, but the granules were not present. Numerous cells presented a clear-cut picture of hydropic degeneration, which has been shown to be a reversible change. Among the cells with hydropic degeneration, there were occasional cells with large clear vacuoles but with the nuclei staining in a homogeneous manner and without chromatic pattern; this appears to be an irreversible change because of the nuclear damage. Mitosis was seen in several islet cells but in no instance was there more than one mitosis in an islet. This complex picture of normal cells, slightly injured cells, and other cells seems best interpreted as a complex response to an injurious agent with some cells capable of survival if the agent is removed, while others are dead and are being replaced by mitotic division of surviving islet cells.

In 1 rabbit, after cessation of injections, the diabetes seemed to disappear, but careful studies over

a period of two and a half months disclosed its persistence. Twenty milligrams of alloxan per kilogram, even if repeated three times a week for seventy-one days, did not produce diabetes, but 40 mg. per kilogram did so if repeated.

Alloxan diabetes was most readily produced in rats by subcutaneous injection. In 2 rats diabetic cataracts developed after two or three months. Diabetic acidosis was rare, but did occur with typical symptoms. In one rat, recovery took place with the help of insulin, but in another, diabetic coma developed, along with extreme polydipsia, a dry tongue, Kussmaul respiration and drowsiness, which finally led to unconsciousness and death.

The rats that received the alloxan intraperitoneally or intravenously instead of subcutaneously showed extensive necrosis of the liver and severe lesions of the kidney, predominantly tubular in type. The rat that received alloxan subcutaneously and developed diabetic coma did not have liver necrosis. Thus it was concluded that the subcutaneous injection of alloxan in doses of 200 mg. per kilogram was a feasible method for producing diabetes in the rat.

* * *

Hughes, Ware and Young¹⁷ found islet-cell changes within five minutes of the subcutaneous ingestion of alloxan into rats. The large islets were not only the first damaged but likewise showed the greatest injury. The initial hyperglycemia ending in hypoglycemia that follows the injection of alloxan was reproduced in rabbits by the injection of adrenalin and protamine zinc insulin equivalent to the amount of insulin known to be present in the pancreas of a normal rabbit—namely, 10 units per kilogram of body weight. A valuable editorial in the same issue of the *Lancet*¹⁸ recalls that Liebig, Lang and others claimed that alloxan could be found in animal secretions and that if alloxan is a constituent of mucoproteins its physiologic significance may be much greater than was ever thought.

INCIDENCE OF DIABETES

Blotner, Hyde and Kingsley¹⁹ report studies in diabetes mellitus and transient glycosuria in 45,650 consecutive selectees and volunteers, aged from eighteen to forty-five years, in the Boston Armed Forces Induction Station. The incidence of diabetes that they found is approximately three to four times that of a nearly similar age group in 1935-1936, ascertained through a house-to-house canvass by the United States Public Health Service. This recent investigation of the incidence of diabetes deserves most careful attention, because the diagnostic methods were sound. Not only was the urine examined, but if sugar was found it was tested before and after lunch on the same day. If the urine repeatedly showed sugar and there was not a verified history of diabetes, the men were sent to an Army hospital for

a 100-gm. glucose-tolerance test carried out after the subjects had fasted all night. Diabetes was diagnosed when the blood-sugar concentration reached a level of 180 mg. per 100 cc., and some or all of the specimens of urine contained varying amounts of sugar. The cases of mild diabetes usually showed normal fasting blood-sugar levels, rising to 200 or 220 mg. per 100 cc. and then falling in two hours to 150 mg. and in three hours to 100 to 125 mg.; those moderately severe presented a fasting level above 140 mg. per 100 cc., with or without glycosuria in the fasting specimen, but the blood sugar reached 275 mg. per 100 cc. and dropped to about 200 mg. in three hours. The severe cases showed a fasting level of about 275 mg., with considerable amounts of sugar in the urine; after the ingestion of glucose the blood sugar rose to about 475 mg. in one hour and dropped only slightly in three hours.

Transient glycosuria was diagnosed in the men who had varying amounts of sugar in the first specimen of urine tested but negative reactions on subsequent days. If, as the writers say, sugar-tolerance tests had been done on all these cases, it is probable that a number of additional cases of diabetes mellitus would have been discovered.

The cases of diabetes mellitus numbered 208, those of transient glycosuria 126, and those of renal glycosuria, as interpreted by the authors, 33.

The average age of the diabetic patients was 34.4 years and of the men with transient glycosuria 27.5 years. The control group averaged 27.5 years. The diabetic patients were on the average (158 pounds) about 18 pounds above the weights of 1000 consecutive selectees (140 pounds) and were of normal average height. Tuberculosis occurred in about the same proportion of the diabetic patients as of the nondiabetic subjects. A diabetic heredity was about six times as frequent in the diabetic patients—32 per cent—as in the nondiabetic subjects used for control—5.2 per cent. No significant variation was noted in the prevalence of diabetes in selectees from communities of different socioeconomic levels or in the prevalence in areas classified by welfare relief paid per capita. The incidence in dense urban areas was 0.8 per cent, as contrasted with 0.4 per cent in the least populated area, and this the writers attribute to the greater proportion of Jews and Irish in the former. Occupation proved to be of little significance. There were twice as many Jews in the diabetic group as in the control group, and nearly half again as many Irish in the diabetic group as in the control group.

I attach great importance to these studies. I have always believed diabetes to be commoner than statistics have revealed. To a slight degree I can confirm the accuracy of diagnosis as performed at various Army hospitals, because many men rejected by the Army, and by the Navy, as well, have later been seen by me for diagnosis and treatment. Of all those re-examined, a difference in diagnosis has probably

normal, were said to have become extremely hard and painful on that day. He had no chills, fever or sweats.

Physical examination showed a slightly distended abdomen. There was generalized voluntary spasm, maximal in the left upper quadrant. No masses were palpable. Peristalsis was normal in pitch but active. Rectal examination was negative.

The temperature was 99.2°F., the pulse 92, and the respirations 20.

Examination of the blood showed a white-cell count of 14,700.

X-ray films of the abdomen showed no free air under the diaphragm. The right half of the diaphragm was slightly elevated. There was an air-filled loop of small bowel in the left upper quadrant that showed a fluid level on standing and was apparently somewhat dilated. No other dilated loops were present. There were scattered areas of gas throughout the abdomen: moderate amounts in the large intestine, and possibly some in the small. The appearance of the abdomen was suggestive of fluid.

The patient was given 500 cc. of blood, as well as plasma and intravenous fluids. A Miller-Abbott tube was passed. Exploratory laparotomy under spinal anesthesia showed a moderate amount of dusky fluid and many white carcinomatous nodules. There were no dilated loops of bowel, no evidence of obstruction, and no leakage around the anastomoses.

Postoperatively the temperature ranged between 99.6 and 100.5°F. The abdominal distention increased. There was no audible peristalsis. The patient complained of pain in the testes and penis. There was considerable vomiting, and occasional hiccoughs. He was given additional intravenous fluids and transfusions. On the third postoperative day he developed jaundice. On the evening of the fifth postoperative day he suddenly went into shock, with profuse sweating and dyspnea. The blood pressure was unobtainable. He was quite distended, and peristalsis could not be heard. He died ten hours later.

DIFFERENTIAL DIAGNOSIS

DR. FRANCIS D. MOORE: Just before the second operation x-ray films were taken. May we see them now?

DR. LAURENCE L. ROBBINS: In this film, taken in the upright position, there are fluid levels and slightly dilated loops of small bowel. The descending colon is visible down to the sigmoid. These loops of small bowel are where the stomach and spleen used to be.

DR. MOORE: Usually in these conferences one is given a history and a physical examination; the patient goes to operation, and one tries to determine the diagnosis. Here we have a patient with two histories, two physical examinations and two

operations, and still we do not know the diagnosis.

Everybody will agree that the fundamental lesion was scirrhus carcinoma of the stomach, and there is no use in spending more time on it. The problem is, What was the nature of the postoperative complication that was fatal?

As we go back over the history we find that at the first operation it was impossible to close the defect in the mesocolon. The esophagus was anastomosed to the jejunum. The duodenum was turned in almost unquestionably, and an enteroenterostomy done — it is not mentioned, but it is virtually routine in this type of anastomosis. The mesocolon coming across in front of the duodenum was brought around anteriorly and the transverse colon had to be cut as part of the operation, a portion being resected including the middle colic vessels. So the patient had another suture line there. He also had a cecostomy.

As to the defect that was not closed — I think that is more or less of a red herring. Following a total gastrectomy, when the jejunum is brought up it is unusual to be able to close the transverse mesocolon. If one did close it around two loops of small bowel, one might get into trouble from the closure because it would tend to cicatrize around the bowel. I should like to know what Dr. Sweet has to say about that. In my experience it is extremely unusual to close the mesotransverse colon in this procedure. Whether that is significant or not I do not know, although there are factors later that suggest that something was going on at the root of the mesentery.

The patient was discharged on the twentieth postoperative day. With such an extensive operation that must mean he had an extremely uneven convalescence. He went home and for six days had occasional "gas pains." If we interpret these pains to mean the smooth-muscle peristaltic cramps of small bowel trying to put a fecal stream through around an obstruction, we must admit that there was something wrong. This is infrequent with gastrectomy of any sort, because the bowel distended to the esophagojejunostomy is not tampered with. It is out of the field of operation, and to have symptoms of small-bowel obstruction lower down is unusual.

On the day of the second admission the patient developed severe pain in the lower abdomen, which spread upward and down the left side. Possibly one should lay stress on the fact that it started below the umbilicus; but it apparently became diffuse and fits in with the concept that he was having smooth-muscle pain in the small bowel. Five hours later he ate supper, after which he became much sicker, which suggests that the obstruction, if it had one, was high up so that eating a meal immediately filled the obstructed loop. When he was admitted he had a slightly distended abdomen and mild spasm, which are compatible with obstruction.

There was no free air, which is comforting. At least there was no perforation.

Then we come to the x-ray examination, which showed air in the large bowel. One might argue that that is evidence against small-bowel obstruction, but it is worth pointing out that with early, high small-bowel obstruction a patient may maintain gas and feces in the large bowel for twenty-four hours before he expels them. Thus, in the first twelve, eighteen or twenty-four hours of high small-bowel obstruction it is possible to find dilated loops as well as gas and feces in the large bowel. Whether the loops in that x-ray film are dilated is open to argument. The haustral markings are coarse, which is characteristic of jejunum rather than of ileum. The finding, however, of frank fluid levels in this area in the vertical position strongly suggests that they are pathologic.

A Miller-Abbott tube was passed. That is interesting because a Miller-Abbott tube could have gone two places in this man: down the esophagus and into the afferent loop or down the esophagus and into the efferent loop, depending totally on the mechanism of the anastomosis. The chances are that it went into the efferent loop, and I think that that is important.

Exploratory laparotomy under spinal anesthesia then showed dusky fluid and white carcinomatous nodules. That is discouraging but probably did not have a great deal to do with what killed him. The dusky fluid in the face of an otherwise negative laparotomy is still compatible with my working diagnosis, because one of the first things that happens in the peritoneal cavity in small-bowel obstruction is the transudation of fluid, and a dusky brown color is characteristic. When they operated on this man, if he had been obstructed, his obstruction had been reduced, or if he had had an internal hernia, it had been reduced, and all they found were the leftovers of the obstruction—nothing that they could remedy. There is no comment on where the Miller-Abbott tube was or how far it went down, but since the patient had no pylorus I assume that it went down a foot or two into the upper jejunum.

DR. GORDON A. DONALDSON: We did not follow it.

DR. MOORE: I think that the findings at operation were compatible with reduced small-bowel obstruction. There was no leakage around the anastomosis. The fact that there was no audible peristalsis postoperatively is of no significance because of the short period of time postoperatively. One would not expect normal peristalsis to get going so soon.

The pain in the testes and penis is hard to interpret, but the lymph, blood and nerve supplies of the testis originate in the somatome that is associated with the kidney. The spermatic arteries come from there, and so it is conceivable that something was going on at the root of the mesentery: tumor, lymphadenitis, torsion or decreased blood supply.

There was considerable vomiting. That is certainly an unusual thing in a person with no stomach in whom a Miller-Abbott tube had been passed. One would not expect vomiting. In the first place it is difficult to visualize because fluid has to run back up from the anastomosis in order for the patient to vomit. That is evidence that there might have been obstruction of a loop into which the Miller-Abbott tube had not passed. This could have been the afferent loop or the loop running from the duodenal closure to the anastomosis.

On the third day the patient developed jaundice. That is an interesting finding. Of course it could have been due to a lot of factors. He could have had carcinoma in the liver sufficiently extensive to give jaundice, or carcinoma around the extrahepatic biliary tree giving obstructive jaundice. But, on the other hand, he became jaundiced with the acute episode and I think it is fair to assume that all of it was part of the same process. Where could he have obstructed a loop of bowel that would produce jaundice? The answer is, The afferent loop. If this loop was obstructed, it is tantamount to obstruction of the common duct, which comes down and enters the afferent loop at the papilla. If that was obstructed, he could not drain bile, would get retrograde pressure back through the papilla and might get jaundice.

On the fifth day he went into shock, with profuse sweating and dyspnea. There are two things that could produce death that rapidly in this man. One is massive intraperitoneal hemorrhage or, as a matter of fact, hemorrhage anywhere. I say "intraperitoneal" because he did not bleed externally. Did he have that? He could have had it, but I do not believe that that is what he had. I think that something perforated and that he died of the shock of a tremendously overwhelming chemical peritonitis. The perforation of a suture line in a portion of bowel that is obstructed below is a much more dramatic and much more shock-producing event than any other form of perforated viscus of which I know. A perforated peptic ulcer classically is supposed to produce shock. Yet of the patients that come to this hospital for perforated peptic ulcer only a very few are in shock. But a patient who is obstructed, "blows out" a suture line and floods his peritoneal cavity with a tremendous amount of intestinal contents, goes into shock and dies rapidly if there is nothing to wall it off.

Can a loop of bowel become obstructed and perforate in this short period of time? It was five days at the most, since we know that the patient did not have obstruction at the second operation. If there were nothing in the bowel to weaken it, such as a suture line or a tumor, I think that the answer is. No. A loop of small bowel may be strangulated for some time before it perforates, and during that period it usually becomes adherent to adjacent loops and may never have free peritoneal perforation.

So that fits in with the general concept that there was obstruction of the afferent loop, which had not been drained by the Miller-Abbott tube, had been reduced at the first operation, had become re-obstructed, had produced jaundice and had eventually blown out one of the three suture lines.

What are the other possibilities? Massive hemorrhage? I do not believe so. Could he have perforated or blown out the suture line in the transverse colon? Yes, but I do not believe that he did. Did he have a completely separate and independent lesion — another carcinoma — that obstructed? Possibly, but there is no evidence for it. Someone may say that thirty-one days after the first operation is too long to have blown out a suture line. It is true that the usual time is seven to ten days, but this man did not have a suture line alone — he had a suture line plus obstruction below it, and the suture line gave out simply because it was the weakest point in the system. Why did he have obstruction of the proximal loop? There are two possibilities. One is that the bowel became kinked at one of the two anastomoses. The other, which is the more likely, is that the patient had a long afferent loop that became herniated into the left upper quadrant behind the efferent loop. That is my diagnosis. He had an obstructed afferent loop — possibly a hernia into the left upper quadrant — that had been reduced at the time of the second operation, became obstructed again and finally blew out the duodenal suture line.

DR. RICHARD H. SWEET: I should like to suggest that the lethal episode that this man suffered was the result of acute pancreatitis. Furthermore, at the second operation it is possible that he might have had an unrecognized pancreatitis.

The other point that I should like to raise is that if Dr. Arthur W. Allen operated on this patient it is unlikely that the patient had a long proximal loop, since that is contrary to his technical method in this type of operation.

DR. MOORE: If the patient had a short proximal loop it would be unlikely that he had a hernia of it. He could, however, obstruct the afferent loop by a kink at the anastomosis.

DR. SWEET: Dr. Allen told me once that he made a great point of placing the enteroenterostomy in this operation as close as possible to the ligament of Treitz.

DR. MOORE: Do you agree that the closure of the mesocolon is unusual?

DR. SWEET: It is in my own practice. I never do it after total gastrectomy.

DR. MOORE: It was possibly a herniation of small bowel independent of the anastomosis, through the rent in the mesocolon; and yet I do not think that is what he had because, as Dr. Sweet has pointed out, it is unusual to close such a rent.

DR. SWEET: I should like to qualify my statement, because this is not strictly a surgical audience.

We do close the rent in the mesocolon in subtotal gastrectomies, but we do not do it in total gastrectomies. Closure of the mesocolon around the loop jejunum is carried out by some surgeons, I am sure, but my own feeling is that it is better not to, or at least that it is unnecessary.

DR. CHESTER M. JONES: I should like to raise question about jaundice caused by obstruction the proximal jejunum or end of the duodenal loop. It must be an unusual occurrence.

DR. MOORE: I saw one patient without biliary tract disease but with an obstructed afferent loop after a subtotal gastrectomy who developed jaundice of a minor order. How much jaundice was there this patient?

DR. BENJAMIN CASTLEMAN: It was reported mild on the ward, but it must have gradually increased because at autopsy there was significant jaundice.

DR. MOORE: He could have had biliary tract disease entirely independent of the acute episode biliary tract disease with obstruction of the duct and perforation of the gall bladder.

DR. CASTLEMAN: Will you elaborate on the second operation, Dr. Donaldson?

DR. DONALDSON: We were reluctant to operate and waited about twelve hours. This we would have done if the patient had not had the operation four weeks previously and undoubtedly present a good many adhesions. Moreover, an x-ray film was taken, which apparently was not reported. Swallow of barium after the first operation showed air-filled loops of bowel in the left upper quadrant. Another reason why we delayed was that the type of pain was unusual. It was lower abdominal pain.

After waiting for twelve hours, however, with a rise in the white-cell count and increased tenderness, we thought that we had to do an exploration. We were quite disturbed to find a small bowel that showed no evidence of obstruction. We were able to put a hand behind the mesocolon and feel the proximal and distal loops, which were not dilated. He did have diffuse carcinomatosis.

DR. MOORE: Did you feel the gall bladder?

DR. DONALDSON: The right upper quadrant was filled with loops of adherent jejunum.

CLINICAL DIAGNOSES

Scirrhus carcinoma of stomach, with metastases to regional lymph nodes and peritoneum.
Operations: total gastrectomy and splenectomy.
Pulmonary embolus?
Acute generalized peritonitis?

DR. MOORE'S DIAGNOSES

Scirrhus carcinoma of stomach, with metastases to regional lymph nodes and peritoneum.
Operations: total gastrectomy and splenectomy.
Small-bowel obstruction.
Rupture of duodenal suture line.
Acute generalized peritonitis.

ANATOMICAL DIAGNOSES

(Scirrhous carcinoma of stomach with metastases to regional lymph nodes.)

Carcinomatous metastases to peritoneum.

Operations: total gastrectomy and splenectomy.

Thrombosis of splenic, portal and superior mesenteric veins.

Mesenteric venous thrombosis, recent.

Infarction of small intestine.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy on this man showed, in addition to a moderately infected abdomen, a loop of small bowel about 100 cm. long that had all the characteristics of infarction and early gangrene. This loop was somewhat bound down and when dissected was located about 100 cm. from the ligament of Treitz. Examination of the mesentery of that loop showed that all the veins were filled with recent thrombi, probably three or four days old. Certainly this loop of bowel was not involved at the time of exploration or it would have been observed. The splenic vein was also completely thrombosed, but this was an old thrombosis — apparently resulting from splenectomy at the time of the first operation. The splenic-vein thrombus extended for a short distance into both the portal and superior mesenteric veins. Within the liver many of the radicles of the portal vein were likewise occluded by thrombi of all ages, which probably accounted for the jaundice. It is possible that during the second operation, in manipulating to try to find the area of obstruction, a small thrombus was broken off, which entered the vein returning blood from the involved loops and caused retrograde thrombosis. Of course, that would have been against the flow of blood, but such a stream may be sluggish, especially in the presence of peritoneal irritation from metastases and infection.

We have seen two other cases in which, following splenectomy associated with a gastrectomy, small thrombi were found in the portal radicles of the liver and in the splenic vein. Perhaps that occurs oftener than we suppose, and the patient gets away with it. In one of these cases the patient died of peritonitis following a rupture of the anastomosis. Perhaps removing the spleen along with a gastrectomy is not without danger. Have you any comment, Dr. Sweet?

DR. SWEET: I have recently given that a lot of thought. I wonder if the thrombosis in the tied-off splenic vein may not be the cause of the so-called "postsplenectomy fever," which often follows splenectomies, especially those performed in cases of Banti's syndrome, whatever that may be. This is a long-lasting fever, which gradually subsides after a period of weeks.

DR. CASTLEMAN: The patient had fever following the first operation but it soon disappeared.

DR. SWEET: This is not at all clear. You have not proved to my satisfaction that the bowel lesion that you discovered existed before Dr. Donaldson's operation, or that it caused pain in the lower abdomen.

DR. CASTLEMAN: Perhaps not at that operation; the gangrene of the bowel was a recent event.

DR. SWEET: Probably following Dr. Donaldson's operation. What was the cause of the symptoms before?

DR. CASTLEMAN: Probably the thrombosis of the splenic vein.

DR. SWEET: Then I should like to ask Dr. Jones if pain from such a thrombosis would be referred to the lower abdomen. I doubt it.

DR. JONES: This patient's pain sounds much more like that of a pancreatitis. I should agree with Dr. Sweet that pain arising from a splenic-vein thrombosis presumably would be high in the abdomen or in the back, or in both.

DR. DONALDSON: It started in the lower abdomen but soon spread to the left upper abdomen.

DR. JONES: Did he have enough carcinomatosis to produce pain?

DR. CASTLEMAN: No.

DR. SWEET: The localization of pain is so important in the making of a diagnosis that in cases of this sort we ought to have it clearly in mind that it often occurs in the upper abdomen.

DR. CASTLEMAN: The final localization of the patient's pain in the left upper quadrant is consistent with thrombosis of the splenic vein.

CASE 30142

PRESENTATION OF CASE

A twenty-seven-year-old Norwegian seaman entered the hospital because of increasing pain in the right hip.

The patient was in perfect health until about five years before admission, when he developed a painful right knee. He was seen by a physician, who told him that his hip was the involved joint. He was treated by bed rest, with great improvement. The pain apparently disappeared until two years before entry when, after being kicked in the thigh, he began to notice pain and limitation of motion in the right hip. He was hospitalized for eight months, after which he was able to return to work. Subsequently, however, the pain increased in severity and there was considerable limitation of movement. He walked with a limp. No other information was available.

Physical examination showed a well-developed and well-nourished man in no distress. The heart, lungs and abdomen were normal. Hip flexion on the right was limited by pain to 90°. Internal and external rotation was limited by pain to 15°. Flexion and extension of the hip produced a grinding motion

and palpable crepitus. There was no discernible atrophy or shortening of the limb.

The blood pressure was 125 systolic, 73 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a white-cell count of 6000, with 70 per cent neutrophils. The hemoglobin was 15.1 gm. per 100 cc. The urine was negative. The sedimentation rate was 12 mm. in sixty minutes. A blood Hinton test was negative.

X-ray examinations of the right hip showed a rounded area of diminished density in the acetabulum and along the superior side of the neck of

of the joint and the flattening of the head. It is quite impressive, particularly in comparison with the previous case,* to see the lack of bone reaction. The decalcification in the right side of the pelvis as well as in the femur is probably on the basis of atrophy. The chest is essentially negative.

DR. REIDY: The adhesions in the chest could have been the result of an infectious process. Is there any evidence of tuberculosis?

DR. ROBBINS: There is possibly some fibrosis in the upper lobes, particularly on the left, but even that is questionable. This could be attributed to old tuberculosis, and the adhesions could be on the basis of an old pleurisy. Certainly there is no evidence of active tuberculosis.

DR. REIDY: This man was relatively young, twenty-seven years old, with quite limited hip function and considerable pain that was sufficient to force him to stop work. He had been hospitalized on several occasions over a relatively long period and the last time he had been immobile for a period of eight months before he was able to get about. On the first occasion we do not know how long he was kept in bed, but it was probably for a fairly long period.

On physical examination there was little other than limitation of motion, described as having been due mostly to pain, but probably also because of the deformity, since one factor rarely causes limitation of motion. It is unusual to see so much atrophy of the bone and none in the soft tissues of the extremities. The description in the physical examination says that he had no discernible atrophy of the thigh.

We have to rule out the possibility of an old slipped epiphysis, which I think is most unlikely since the hip was in relatively good position, although it could have slipped slightly, in that the anterior lip in this film is a little low. That could produce traumatic arthritis due to faulty mechanics of the hip joint.

Legg-Perthes's disease is a possibility, but more broadening of the head and flattening would be expected in that condition. The lesion in question shows narrowing of the joint space. In addition to the diminished density in the acetabulum there is also some evidence of destruction in the head of the femur, which could be the result of a disease process crossing the joint or just due to disuse. It could occur, however, as the result of trauma.

Gout is most unlikely. Nothing is said of an elevated blood uric acid, and the x-ray picture is, I believe, unlike it; although I have seen a case somewhat similar to this, in which a gouty nodule was removed from the capsule of the hip joint. A malignant neoplasm is also unlikely since, after five years, one would expect more destruction than we see here.

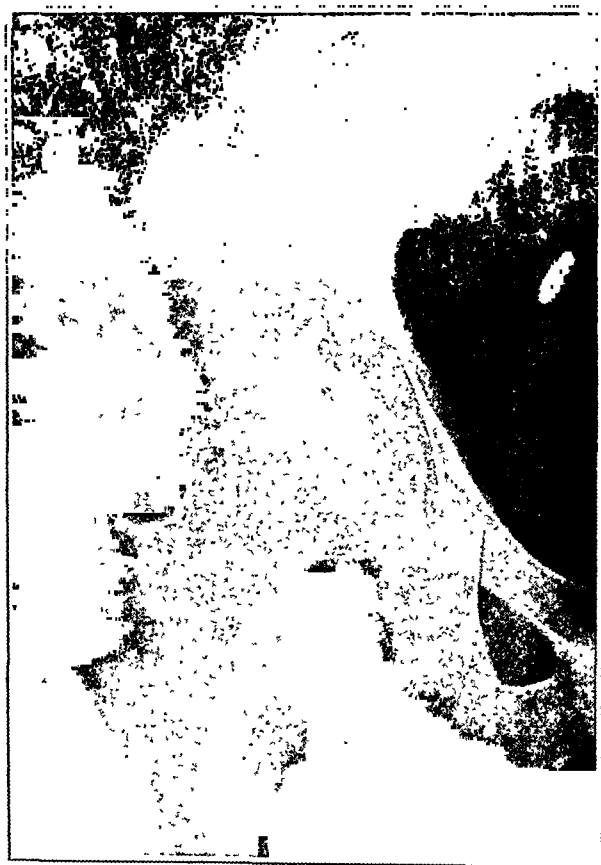


FIGURE 1. Roentgenogram of Right Hip Joint.

the right femur, with very little bone reaction (Fig. 1). The joint spaces were slightly narrowed, but the joint surfaces were intact. The head of the femur showed some flattening. In the lateral view the shaft displayed moderate atrophy and coarse trabeculation. X-ray films of the chest were negative except for adhesions to the left diaphragm.

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JOHN REIDY: We might start by looking at the x-ray films.

DR. LAURENCE L. ROBBINS: These are the areas of rarefaction that were described, with the narrowing

*Case records of the Massachusetts General Hospital (Case 3013) *New Eng. J. Med.* 230:409-412, 1944.

A low-grade inflammatory process, I believe, is the thing that must be considered. There is no help so far as blood count or sedimentation rate is concerned.

Osteochondritis dissecans, again the result of trauma, is a possibility, particularly in view of the fact that they mention a grinding sensation, which might mean that a portion of the acetabulum or head of the femur had been broken off into the hip joint, although the crepitus might well be accounted for by the irregularity and the defect in the acetabulum.

I believe that we should also consider xanthoma or Gaucher's disease. I have seen a case of Gaucher's disease with a lesion in the acetabulum similar to this that did not cross the joint and therefore had produced no change in the head of the femur.

In a young man of twenty-seven it is unusual to have a traumatic arthritis of this degree. I should think that he probably had a low-grade infection, since there is no evidence of anything acute, and a tuberculous lesion should be seriously considered. Tuberculosis of the acetabulum does occur but less frequently than does tuberculosis of the head. X-ray evidence of involvement of the head, with a moderate degree of atrophy and destruction, should permit us to consider tuberculosis as a thoroughly tenable diagnosis.

There is another unusual lesion that might be mentioned in this case, in view of the fact that he was a seaman. Had he done any diving?

DR. MARIUS N. SMITH-PETERSEN: In spite of the history, he was not a seaman.

DR. REIDY: If he had been a diver, caisson disease might be considered. Sometimes the vessels in the terminal portions of the bone become occluded and an aseptic necrosis results, with a picture similar to this and destruction of the joint as the lesion goes on.

To summarize, this man had a fairly extensive lesion in the hip, considerable atrophy of the bone about the hip joint, a definite area of bone destruction in the acetabulum and another area of destruction in the head of the femur, with narrowing of the joint. The fact that he improved with long periods of rest, only to have recurrences, is suggestive of a low-grade infection, and I make tuberculosis my first diagnosis rather than a neoplastic type of lesion.

DR. SMITH-PETERSEN: One cannot afford to be little the changes in the head and neck of the femur,

because there was distinct change in the architecture of the two. The changes in the epiphyseal line are perfectly consistent with several epiphyseal slips. The patient had symptoms at the age of twenty-one. At that time he was beyond the stage of a slipped epiphysis, but in skiing he must have been exposed to trauma and could have had minor slips earlier in life to which he paid little attention. After twenty-one, he had symptoms perfectly consistent with faulty architecture and at that time was in bed for six or seven months.

Our preoperative diagnosis was traumatic arthritis secondary to faulty architecture, which would account for the changes in the acetabulum. Whether it began as cystic degenerative change, we did not know. At the time of operation, on approaching the joint, the anterior acetabulum was cut through and the cut went across those areas that you see, which contained pink gelatinous material. There was some discoloration of the adjacent articular cartilage. The changes in the head were perfectly similar to the changes that one finds in *malum coxae senilis*, in which there are cystic areas; but that is not what these areas represented. To call them cysts is hardly correct. They were degenerative fatty areas that when squeezed oozed material similar to olive oil. There was villus change in the inferior compartment but the villi were not the ordinary type. The joint did not have the appearance of a joint that was or had been infected, nor did it resemble tuberculosis in any way, shape or manner. The postoperative diagnosis was traumatic arthritis, and a cup arthroplasty was done.

CLINICAL DIAGNOSIS

Traumatic arthritis.

DR. REIDY'S DIAGNOSIS

Tuberculosis of acetabulum, head of femur and hip joint.

ANATOMICAL DIAGNOSIS

Tuberculosis of hip.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Microscopic examination of the synovial lining of the joint, as well as that of the bone of the head of the femur, showed tuberculosis.

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HOSPITALIZATION FOR ACUTE COMMUNICABLE DISEASES

THERE are many good reasons for reconsidering the role of special contagious-disease hospitals. In recent years a definite change in attitude toward certain diseases has occurred, and they have been taken out of the class of those that are considered suitable for isolation in special hospitals. An example of immediate interest is meningococcal meningitis. In the past, cases of this disease have been considered especially suitable for care in isolation hospitals but now they are being treated in the wards of general hospitals without difficulty. The problem of isolation and quarantine in cases of scarlet fever has been considered in a recent edi-

torial in the *Journal*.¹ It is quite incongruous in the light of present-day understanding of streptococcal infections to consider scarlet fever as the only one of a group of hemolytic streptococcus diseases that requires isolation in special contagious-disease hospitals, while patients with tonsillitis or septic wound infections are treated in the open wards or in single rooms of general hospitals. Smallpox may be considered as an extreme example. "even with this disease the facts that . . . tion against it is practically universal and that the immunity of the hospital personnel can be maintained by frequent revaccination make it perfectly feasible to treat cases of this disease in single rooms of general hospitals.

General hospitals are, willingly or otherwise, treating cases of all sorts of communicable diseases at the present time. Many patients are admitted before the correct diagnosis is made and when they are presumably at the height of their contagiousness and when the possibility of communicable disease is entertained, the staff of the hospital must be prepared to use proper technic to avoid transfer of infection to themselves and to others. This makes quite essential for the entire staff to be acquainted with the technics that limit the spread of contagious diseases.

The diagnosis and care of open cases of tuberculosis, although different in many respects from those of other acute communicable diseases, present some problems along the same line. The hospitals for the care of such cases are crowded, and even when beds in such institutions are available, many patients are loath to take advantage of their facilities. General hospitals, particularly large municipal hospitals, are constantly called on to receive such patients and to hold them for long periods, pending their final placement in suitable institutions. During this time, the open cases of tuberculosis are in many ways similar in their contagiousness to other cases of the more acute infectious diseases. Arrangements for their management should be adequate to minimize the spread of disease among the hospital contacts, and such arrangements are nowise different from those necessary for the care of patients with other communicable diseases.

Another factor to be taken into account, particularly in this part of the country, is the steady increase in the burdens that the general hospitals are carrying. All physicians in large cities are constantly troubled with the inability to obtain hospital facilities for those among their patients who require care that cannot be given in the home. The overcrowding of these hospitals is due, in large measure, to the increase in popularity of the agencies that provide hospitalization insurance. In the future it is to be expected that hospital insurance will become more rather than less popular and that the burden on the general hospitals will consequently increase.

The specialized hospitals for contagious diseases, on the other hand, are not being used to capacity. Even during epidemics the use of their facilities is only temporary. The staffs of such hospitals are necessarily large, and a good part of the staff must be maintained even when this is not warranted by the number of cases. Furthermore, because of the wide fluctuations in use, their facilities are often permitted to deteriorate, and the aid of modern equipment and treatment, which is available in general hospitals, is often denied to patients.

The present problem of the shortage of nurses may provide a good excuse for the immediate consideration of this important problem. Contagious-disease hospitals require a relatively greater number of nurses per patient than do general hospitals and much of the time a large percentage of these nurses are not working to capacity, general hospitals, on the other hand, are much understaffed and their nurses are greatly overworked.

The objection that provisions must be made for the emergencies incident to epidemics does not provide an argument for the maintenance of special contagious-disease hospitals. General hospitals should be able to expand their facilities for the emergencies provided by disasters, and epidemics may well be classed in a group with other disasters. The reorientation of existent communicable-disease hospitals to serve within the framework of the general hospitals, although it might not entirely alleviate the nursing and bed situation, would undoubtedly be of some help. The views of the New York State Department of Health² on this subject

have recently been summarized at the request of a group of hospital administrators and health officers and are worth quoting.

In the early part of this century, there was a tendency on the part of municipalities to build special hospitals for the isolation of communicable diseases. These so called 'pest houses' were designed particularly for the care of smallpox cases but were intended for the isolation of other acute infectious diseases as well. At that time, it was thought feasible to control communicable diseases in communities through isolation of recognized cases since it was felt that if all patients were isolated until they were no longer infectious, the spread of these diseases would cease. However, upon further investigation from a bacteriological standpoint it was learned that in many communicable diseases symptomless carriers and atypical cases which ordinarily would not be recognized as infectious are frequently more important in the spread of the disease in the community than the typical cases which can be detected. The routine hospitalization of acute communicable diseases for the sole purpose of limiting spread of the infection in the community, therefore, obviously would not accomplish this objective.

At present, hospitalization of contagious diseases ordinarily is recommended only in those cases requiring care from the standpoint of the welfare of the patient himself and which can be given only in a hospital and not at home. In rare circumstances, it may still be necessary to hospitalize patients from the standpoint of the protection of the community as, for example, in the case of a communicable disease discovered in a transient or occurring in a home in which for certain reasons proper isolation is impossible.

Concomitant with the development of our bacteriological knowledge of communicable disease, techniques have been devised to permit the safe isolation of cases of communicable diseases in general hospitals. These procedures vary with the disease; some patients can be cared for without danger on a ward, others must be confined to a private room. However, there is essentially no communicable disease which cannot be cared for safely in a private room on a floor on which there are other patients with noncommunicable diseases, providing certain techniques are practiced rigidly by the attendants. It has become increasingly clear that the training and skill of the attendants are much more important in controlling the spread of infection than the physical equipment provided.

In the opinion of the New York State Department of Health, therefore, separate buildings for the sole care of communicable diseases are not essential. In larger municipalities it may be more convenient for a hospital to have a separate building for this purpose but this is a matter of convenience and not necessity. In smaller places in which such a building would be vacant a large part of the time, an unnecessary expense to the community would be entailed.

Every hospital is dealing with communicable diseases whether or not it recognizes that fact. Because of the prevalence of carriers and atypical cases among the general population, it is inevitable that such carriers and cases will be admitted from time to time to a hospital even though the infection is not detected at the time of admission. The routine procedures followed in these hospitals, therefore, with regard to the hygienic practices of the

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The diagnosis and care of open cases of tuberculosis, although different in many respects from those of other acute communicable diseases, present some problems along the same line. The special hospitals for the care of such cases are overcrowded, and even when beds in such sanatoriums are available, many patients are loath to take advantage of their facilities. General hospitals, particularly large municipal hospitals, are constantly called on to receive such patients and to keep them for long periods, pending their final placement in suitable institutions. During this time, the open cases of tuberculosis are in many ways similar in their contagiousness to other cases of the more acute infectious diseases. Arrangements for the management should be adequate to minimize the spread of disease among the hospital contacts, and such arrangements are nowise different from those necessary for the care of patients with other communicable diseases.

hours to tell me that a boy was having convulsions. He had broken his ankle three days before, and she suggested that he might have had an embolus to explain the convulsions. She said his respirations were 58 and his pulse rate 60! Leaving several patients in the office I dashed to the school at sixty miles an hour to find the boy asleep and, when waked up totally oblivious that anything was wrong with him. His pulse was 76 and his respirations were 16. I became incoherent and if I said anything it was only to mention the name of the deity over and over. After she saw that I was unsympathetic to the embolism theory, she suggested it might be epilepsy. I tore my hair again, but it did no good.

A few days later she again called me up — "urgently" — to tell me that a boy whose ankle I had strapped had suffered agonizing pain" all night, that the strapping had caused great swelling and that he had paralysis of the foot and ankle. She had me worried, because I did not believe that she knew enough to make up such a story. I had visions of meeting the boy's parents face to face and trying to explain how I had not caused the paralysis, how these things happen once in a while and how extremely unfortunate it was. I was willing to admit that perhaps I had put on the strapping a little too tightly. So in an agonized frame of mind I made my way to the school to find a foot that was normal in every respect except for the swelling caused by a badly sprained ankle.

A while ago there was a measles epidemic. Every day there were three or four new cases. Toward the end of the epidemic the nurse became tired and nervous, and her mind which normally was extremely excitable had reached the explosive stage. While walking with her across the campus she told me she had found a dead rat. I did not say a word. I knew what was working in her mind. Sure enough, the next day the wires began to burn again and after paging me over the countryside she at last got me on the telephone. There are two more down," she said, "I don't like it, I don't like it. I think you ought to come to the school immediately. I took my time in getting there, and on arrival found that another doctor had preceded me. I asked her what all the excitement was about. She wouldn't tell me but I knew she had made the diagnosis of bubonic plague!

And so I live from day to day, almost in a state of collapse with the sword of Damocles hanging by a thread above my neck.

\\ C S

NOTICES

POSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists will be held at the Surgical Amphitheater (3A) of the White Building Massachusetts General Hospital, on Wednesday, April 19 at 8 p.m.

PROGRAM

- The Physical-Chemical Properties of the Plasma Proteins and Their Concentration into Fractions of Differing Functions. Drs E. J. Cohn, L. E. Strong, J. L. Oncley, W. L. Hughes, Jr., and S. H. Armstrong, Jr.
- Fibrinogen and Thrombin and the Products Derived from Them. Drs J. D. Ferry, J. T. Edsall, E. A. Bering Jr., and P. R. Morrison.
- Immunological Studies on the Plasma Proteins. Dr. J. F. Enders.
- Clinical Investigations with Albumin and Immune Globulins. Drs C. A. Janeway, L. Woodruff and C. Ordman.
- Clinical Investigations with Products of Fibrinogen and Thrombin. Drs O. T. Bailey and T. D. Ingraham.

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association 554 Columbus Avenue Boston on Tuesday, April 18 at 12 m. Dr. Vlado A. Getting will speak on the subject, "Tropical Diseases".

Physicians are cordially invited to attend.

MASSACHUSETTS CENTRAL HEALTH COUNCIL

Featuring a panel entitled "Should Social Security Be Extended Farther into the Fields of Medical Care and Hospital Service?" the annual meeting of the Massachusetts Central Health Council will be held at the Pioneer Y W C A, 140 Clarendon Street, Boston, promptly at twelve noon on Friday, May 5. After a buffet lunch (80 cents) and a brief business meeting the panel discussion with the president Dr. George C. Shattuck acting as chairman will proceed.

G. F. Houser, M.D., first assistant director, Massachusetts General Hospital, and Walter G. Phippen M.D. member of the Massachusetts Medical Society.

Nurses and social workers, as well as physicians are cordially invited to attend. Luncheon reservations should be sent to the secretary, Arthur J. Strawn 1148 Little Building Boston 16.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGY

The next meeting of the New England Society of Anesthesiology will be held in the Bigelow Amphitheater of the Massachusetts General Hospital on Tuesday, April 11, at 8 p.m. Dr. K. M. Heard will speak on the subject, "Benefits and Hazards of Pentothal".

NEW ENGLAND DERMATOLOGICAL SOCIETY

The annual meeting of the New England Dermatological Society will be held in the Skin Out Patient Department of the Boston City Hospital on Wednesday April 12, at 2 p.m.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

A meeting of the New England Ophthalmological Society will be held at the Massachusetts Eye and Ear Infirmary 243 Charles Street, Boston, on Tuesday, April 18, at 8 p.m.

Following the business meeting John Marquis Converse a major in the Medical Corps of the French Army, will show a motion picture. Dr. Walter B. Lancaster will then speak on the subject "Some Chestnuts from My Stock Pile".

NEW ENGLAND OTOLARYNGOLOGICAL SOCIETY

The regular spring meeting of the New England Otolaryngological Society will be held at the Massachusetts Eye and Ear Infirmary on Wednesday, May 10.

NEW ENGLAND PATHOLOGICAL SOCIETY

The annual meeting of the New England Pathological Society will be held at the Harvard Club Boston on Thursday, April 20. Following the dinner at 6 p.m., Dr. Tom Spies will speak on the topic, "Pathological Changes Occurring in Certain Vitamin Deficiencies in Man".

UNITED STATES CIVIL SERVICE COMMISSION

While on battlefronts scattered throughout the world our Armed Forces are concentrating on winning the war, in Army and Veterans' hospitals here in the United States trained occupational therapists are among those lending their efforts toward winning the peace.

These therapists are erasing the ravages of war by the systematic rehabilitation of injured bodies and minds. Some

of the war-wounded are reconditioned for further service in the Army; others are fitted for useful civilian work in a normal environment.

As increasing numbers of injured soldiers return to the hospitals, more and more occupational therapists are needed to aid in their adjustment to normal life. In greatest demand are experienced graduates of accredited schools of occupational therapy. Experience should be in hospitals acceptable to the American Medical Association. For some positions, however, college training in psychology and in arts and crafts or trades and industries, or experience as a junior aide in Veterans' hospitals, may be substituted for training in occupational therapy schools. Other positions will be filled by inexperienced graduates of occupational therapy schools.

The salary range of these positions is \$1970 to \$2433 a year, including overtime pay. Those appointed at \$1970 will be trainees for a period of eighteen months; those appointed at \$2190 and \$2433 will administer occupational therapy under medical and general supervision in Army and Veterans' hospitals.

There are no age limits and no written tests, but applicants must be physically capable of performing the duties involved. Persons now using their highest skills in war work should not apply. Federal appointments are made in accordance with War Manpower Commission policies and employment stabilization programs.

Further information on occupational-therapy aide positions and forms for applying can be obtained from first-class and second-class post offices or from the United States Civil Service Commission, Washington 25, D. C.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 13

THURSDAY, APRIL 13

*9:00-10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

FRIDAY, APRIL 14

*9:00-10:00 a.m. Treatment of Amputees in the Services and Later. Rear-Admiral R. H. Laning (MC), U.S.N.R. Joseph H. Pratt Diagnostic Hospital.

SATURDAY, APRIL 15

*10:00-11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, APRIL 17

*12:15-1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, APRIL 18

*9:00-10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Tropical Diseases. Dr. Vlado A. Getting. South End Medical Club. Headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

*12:15-1:15 p.m. Clinicorontgenological conference. Peter Bent Brigham Hospital.

WEDNESDAY, APRIL 19

*12:00 m. Clinicopathological conference. Children's Hospital. 8:00 p.m. Boston Society of Biologists. Surgical Amphitheater (3A) of the White Building, Massachusetts General Hospital.

*Open to the medical profession.

APRIL 11. New England Society of Anesthesiology. Page 443.

APRIL 12. New England Dermatological Society. Page 443.

APRIL 13. The Use and Misuse of Bacterial Chemotherapy. Dr. Charles A. Janeway. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

APRIL 18. New England Ophthalmological Society. Page 443

APRIL 20. New England Pathological Society. Page 443.

APRIL 24 and 25. Massachusetts Safety Conference on War Production and Civilian Defense. Page ix, issue of March 30.

APRIL 29. Long Island College of Medicine. Page ix, issue of March 30.

MAY 5. Massachusetts Central Health Council. Page 443

MAY 8-14. War Conference on Industrial Medicine, Hygiene and Nursing. Page x, issue of March 23.

MAY 10. New England Oto-Laryngological Society. Page 443

MAY 23 and 24. Massachusetts Medical Society. Annual meeting Hotel Statler, Boston.

JUNE 7-13. American Board of Obstetrics and Gynecology. Page x, issue of March 23.

JUNE 12-16. American Medical Association. Annual meeting, Chicago. Page 798, issue of November 18.

JUNE 12-16. American Physicians' Art Association. Page x, issue of March 2.

OCTOBER 3-5. American Public Health Association, Hotel Pennsylvania, New York. Page ix, issue of March 30.

DISTRICT MEDICAL SOCIETIES

SUFFOLK

MAY 4. Censors' Meeting. Page xiii, issue of February 10

WORCESTER

APRIL 12. Hahnemann Hospital, Worcester.

MAY 10. Annual meeting.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

American Standard Definitions of Electrical Terms. 4°, cloth, 311 pp. New York: American Institute of Electrical Engineers, 1943. \$1.00.

This authoritative reference work was compiled by a special committee representing thirty-three organizations in the electrical field and organized by the American Institute of Electrical Engineers. The committee was enlarged by the appointment of eighteen subcommittees with a total membership of one hundred and twenty, to which were added numerous nonmember experts, so that, in all, over three hundred authorities in all fields aided in the compilation. The primary aim of this glossary is to express for each term the meaning that is generally associated with it in electrical engineering in the United States. The preferred definition is a simple one, with a single statement of function rather than explicit description of all properties included and excluded. The arrangement is by special groups and subsidiary sections. The numbering used to identify terms is based on a system proposed for use by the International Electrotechnical Commission. Groups 75 and 80, having to do with radiology and electrobiology, including electrotherapeutics, are of medical interest. There is an extensive, comprehensive index. The work is well arranged and well printed on good paper in a good binding and sold at a nominal price. It should be in all medical libraries, as well as in the offices of all physicians interested in radiology and electrotherapeutics.

Lincoln-Douglas: The weather as destiny. By William F. Petersen, M.D. 8°, cloth, 211 pp., with 16 illustrations. Springfield, Illinois: Charles C Thomas, 1943. \$3.00.

The author contends that the relation between the human body and the atmosphere in which it functions is of primary importance and that this relation must be understood if man is to make any progress in adjusting himself to the inexorable conditions of existence. His thesis has been built around the famous Lincoln-Douglas controversy.

Medical Clinics on Bone Diseases: A text and atlas. By I. Snapper, M.D. 4°, cloth, 225 pp., with 30 plates and 39 tables. New York: Interscience Publishers, Incorporated, 1943. \$10.75.

In this book are presented observations and x-ray pictures especially chosen to elucidate some of the problems involved in the recent expansion of knowledge of bone diseases. The comparison of experiences is made between conditions in the Western Hemisphere and those in China.

The manner of injury to the head was in most cases remarkably similar. Eighteen patients (46 per cent) had fallen downstairs or on paved streets, a type of accident especially frequent among alcoholic patients. Full details concerning such accidents were rarely obtainable, since most of these patients were found lying on the sidewalk in a comatose condition. Traffic accidents were responsible for the next largest group (36 per cent), and a variety of incidents accounted for the remainder.

DEFINITION OF TERMS

The duration of the post-traumatic psychosis, its intellectual, emotional and personality disturbances, may extend well into weeks or months and the end is often difficult to define. The period of disorientation can be more definitely delimited, and in these cases was ascertained by asking specific questions pertaining to time, place and situation, repeated at daily intervals. For the purposes of this study it was therefore found convenient to regard confusion as synonymous with disorientation in one more spheres, and the data have been arranged according to the duration of such confusion. Coma and semicomatose were considered ended when the patient was able to respond recognizably to calling name.

In Table 1 the frequency of abnormal signs is listed. In Tables 2 and 3 a number of findings are analyzed with regard to their duration. Short, medium and long periods of confusion were arbitrarily chosen so that a similar number of cases in each group would be available for comparison. The separate listing of patients who died was dictated by the fact that death rather than recovery terminated the end of the confusion, and only those patients who died after three days have been included. The temperature, pulse and respirations were considered to have returned to normal when elevations of these vital signs did not exceed the accepted norm¹⁰; in addition, the occurrence of abnormally high or low values was noted. Blalock's¹¹ definition of surgical shock was followed. Many normal abnormal findings were obtained on neurologic examination, but only Babinski's sign and clonus or absence of tendon reflexes occurred with sufficient frequency to be tabulated. Focal or generalized disturbances of frequency in the electroencephalographic tracings were regarded as attributable to the head injury, in accordance with the criteria of studies reported in the literature.¹² Some of the terms used are self-explanatory, but others demand arbitrary definition. Acute alcoholism was recorded when the odor of alcohol on admission was substantiated by a history of considerable intake immediately before the accident, habitual use of alcohol to excess, with frequent arrests for drunkenness or a history of delirium

tremens, was considered evidence for alcoholism. Apathy was defined as a state in which the patient shows no interest in his own condition, his physician or his surroundings. The period during which the patient could not respond to psychologic tests was measured by ability to co-operate in such simple tasks as serial subtraction or study of absurd pictures. Data regarding the manner in which the response to such psychologic tests is disturbed following head injury have been analyzed and presented elsewhere.¹³ The ability to co-operate in any degree in such tests is here recorded as a stage in the recovery process. Drowsiness was regarded as a condition in which the patient tends to fall asleep repeatedly during the ordinary waking hours. In hospital records such variable states as semicomatose, confusion, apathy and lack of speech are often described as stupor. We have used this word to describe those patients who were able to eat or drink and maintain body position but failed to give any verbal responses. The term "incoherence" is used to describe the condition, irrespective of its etiology, in which speech was disorganized, reaching the extreme in a confused mixture of words. In this study the use of the term "perseveration" has been limited to repetition in speech. An abnormal sense of well being has been described as "euphoria," and a morbid impulse to joke as "mania." Patients who had difficulty in adjusting to the hospital environment after they were sufficiently recovered to be ambulatory on the ward were considered behavior problems.

In evaluating the status during the immediate follow-up period, dementia was adjudged to be present when disorientation still existed after three months. In those patients designated as intellectually impaired, the psychometric findings were well below the range that could be expected from the school and occupational histories. Except where actual measurements such as those of pulse, temperature, respirations and spinal fluid pressure could be used, only the presence or absence of certain features was noted, since the degree was a matter of interpretation.

CLINICAL DATA

Frequency of Signs

The principal abnormal findings are presented in order of frequency in Table 1. Abnormal electroencephalographic findings (93 per cent), bloody spinal fluid (90 per cent) and elevated spinal-fluid pressure (74 per cent) occurred in the great majority of cases. Babinski's sign (67 per cent) and skull fracture (65 per cent) were next in frequency. This tabulation focuses attention on the high incidence of the presumptive evidences of severe brain damage in patients with prolonged confusion as a result of head injury.

Many compound or depressed skull fractures, together with the intracranial hemorrhages, re-

We are indebted to Dr. Charles Brenner for the electroencephalographic

counted for the large number of operations in this series. The frequency of subdural or extradural hemorrhage (27 per cent) indicates that these complications should be carefully considered in con-

TABLE 1. Frequency of Abnormal Findings.

FINDING	FREQUENCY
Abnormal electroencephalographic findings	93
Bloody spinal fluid	90
Pressure above 200 mm. of water on lumbar puncture	74
Babinski's sign	67
Skull fracture	65
Restlessness	64
Acute alcoholism	60
Respiratory rate above 30	51
History of chronic alcoholism	50
Abnormalities of tendon reflexes	49
Perseveration	48
Maximal fluctuation of diastolic blood pressure above 40	47
Pulse rate above 120	46
Pulse rate below 60	41
Confabulation	39
Maximal fluctuation of systolic blood pressure above 60	38
Dysphasic disorder of speech or perception	36
Skull operation	36
Apathy	33
Temperature above 103°F.	31
Irritability	28
Subdural or extradural hemorrhage*	27
Behavior problem	26
Stupor	23
Complicating extracranial injuries	20
Incoherence of speech	18
Convulsions	15
Hallucinations	14
Surgical shock	11
Euphoria and moria	10

*Verified by operation or autopsy.

fused patients. During their early hospital course 15 per cent of the patients experienced convulsive seizures.

Intellectual disturbances, such as perseveration, confabulation and dysphasic disorders, outnumbered other mental abnormalities. Ten patients (26 per

It is worth noting that a great number of signs were comparatively infrequent in the patients in whom the duration of confusion was short (Table 2). Patients disoriented for less than twenty days did not have convulsions or incoherence, although the incidence (40 to 60 per cent) was fairly high in those confused for twenty-one days or over. Likewise, neither stupor nor a temperature above 103°F. was found in patients disoriented for less than ten days. In contrast to these findings, there were signs that were no less frequent in the patients in whom confusion was of short duration. Among these were abnormal electroencephalograms, Babinski's sign, significant respiratory, pulse and blood-pressure changes, complicating extracranial injuries and surgical shock. Apathy, euphoria and moria were actually more frequent in the patients who were disoriented for less than ten days than in others.

Acute and chronic alcoholism occurred in well over half the cases. The mean duration of confusion in the alcoholic group (nineteen days) was considerably longer than that in the nonalcoholic group (eleven days). It should be pointed out, however, that the mean age of the alcoholic patients was also greater than that of the other subjects (forty-six as compared with thirty-one years).

Not mentioned in the tables were the following features that occurred in relatively few cases. Eight patients (21 per cent) had a history of previous head injury. Three showed a lucid interval between an initial and later period of confusion, and 2 exhibited marked fluctuation in the level of consciousness. Four of these 5 patients were found to have sub-

TABLE 2. Changes in Frequency of Findings With Decreasing Duration of Confusion.

DATA	ALL CASES	DEATH AFTER 4-23 DAYS	21 DAYS OR LONGER	DURATION OF CONFUSION 10-20 DAYS	3-9 DAYS
Number of cases	39	5	10	12	12
Mean age (years)	39	52	41	48	24
Decreased incidence (percentage):					
Bloody spinal fluid	90	100	100	91	75
Pressure above 200 mm. of water on lumbar puncture	74	80	90	82	50
Skull fracture	65	80	80	55	50
Restlessness	64	60	80	58	58
Acute alcoholism	62	60	70	67	42
History of chronic alcoholism	50	40	60	58	36
Perseveration	48	40†	89	50	16
Confabulation	39	20†	56	58	8
Dysphasic disorder of speech or perception	36	25†	80	25	8
Skull operation	36	40	60	25	25
Temperature above 103°F.	31	80	40	31	0
Irritability	28	—	60	17	25
Behavior problem	26	—	70	8	17
Stupor	23	40†	50	17	0
Subdural or extradural hemorrhage*	27	75	30	27	17
Incoherence	18	20†	60	0	0
Convulsions	15	40	40	0	0
Increased incidence (percentage):					
Apathy	33	—	30	25	58
Euphoria and moria	10	—	0	25	8

*Verified at operation or autopsy.

†The percentage given is that of the total number of cases, regardless of whether death supervened before normality had returned.

cent) presented behavior problems on the ward. Apathy and marked irritability were encountered in about a third of the cases. Hallucinations were relatively rare (14 per cent), and with the exception of 1 case occurred only in acute or chronic alcoholic patients.

dural hematomas, and in the fifth the right frontal lobe had been traumatically amputated. The 3 patients with dementia exhibited an abnormally increased appetite.

The 5 patients who died during their initial hospitalization represented particularly severe head

uries with complications. Four had sustained all fractures — 3 basilar and 1 compound. All had perience contusion and laceration of the brain.

The 4 with subdural hemorrhages, 3 died within the first six days, 2 of them despite operation; the fourth lingered for twenty days, finally dying of septicemia. A seventy-two-year-old man lived for twenty-three days and developed an acute terminal meningitis with epileptiform seizures. At autopsy it was found to have an old *plaque jaune* with a large area of recent softening, in addition to some contusion and laceration. One patient was explored a second time for a subdural hematoma when he failed to improve after removal of a large subdural hemorrhage, but only an extensive area of softening was discovered. An elderly woman with a compound skull fracture, multiple fractures, early surgical shock and subdural hemorrhage remained in coma for six days before death.

Duration of Signs

The mean duration of the various findings is shown in Figure 1. The ability to speak returned early, on an average during the first day, and usually immediately after the reappearance of reflex activity as coma subsided. The first response to simple psychologic tests was not attained until the second week, but this degree of improvement was preceded by correct orientation in place, situation and time. Of the vital signs, the respirations returned to normal first, then the temperature and last the pulse. As might be expected, the duration of abnormal signs varied directly according to the duration of confusion, although pulse fluctuation was an exception to this general rule.

In Table 3 it will be seen that the order of events in recovery varied in the three groups of confused

to those with less prolonged confusion. Restlessness requiring restraint lasted relatively longer in the patients with moderate durations of confusion than in those with shorter or longer disorientation.

None of the patients who died responded to the simplest psychologic tests before death, and 80 per

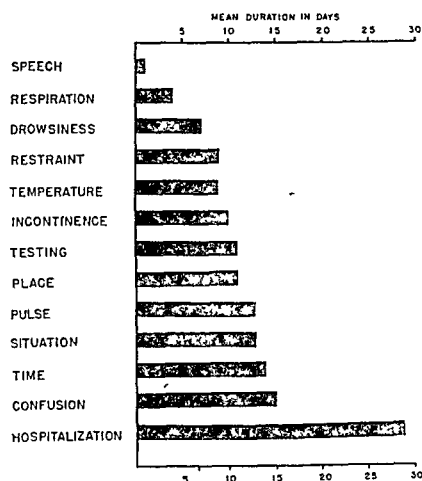


FIGURE 1. Duration of Abnormal Signs in 39 Cases with Prolonged Confusion following Head Injury.

cent of those longest confused were not testable during hospitalization. Only 13 per cent of those disoriented for ten to twenty days were completely incapacitated in this respect throughout their stay, whereas subjects with the shortest confusion could

TABLE 3. Duration of Abnormal Findings According to Duration of Confusion

FINDING	ALL CASES	DEATH AFTER 4-23 DAYS*	DURATION OF CONFUSION		
	day	day	21 DAYS OR LONGER	10-20 DAYS	3-9 DAYS
Lack of speech	1	2	2	1	1
Abnormal rate of respiration	4	10	6	4	2
Drowsiness	7	6	9	8	5
Restraint	9	13	17	8	2
Abnormal fluctuation in temperature	9	14	11	9	2
Incontinence	10	13	19	7	4
Inability to respond to tests	11	13	24	6	4
	11	13	29	7	4
	13	12	15	10	5
	13	13	11	12	6
	14	13	33	5	10
Hospitalization	29	12	41	34	22

*In the patients who died many signs persisted until death, and the duration of the sign in each case was the same as for the period from injury to death. The mean duration was calculated, nevertheless, in order to show that some signs persisted longer on the average than did others, even when death supervened.

patients who ultimately recovered. The variations chiefly concern the duration of abnormalities in respiration, temperature and pulse. The order of recovery from speechlessness, incontinence and disorientation in place, situation and time was the same in all. Drowsiness persisted longer in relation

to those with less prolonged confusion. Restlessness requiring restraint lasted relatively longer in the patients with moderate durations of confusion than in those with shorter or longer disorientation. None of the patients who died responded to the simplest psychologic tests before death, and 80 per

studied at this hospital, regardless of duration of confusion, approximately 2 per cent of all patients had marked and probably permanent intellectual defect at the end of three months.

All 14 cases listed under the heading of dysphasia suffered from impairments in perception and execution associated with confusion. Understanding of

light of the long disturbances of consciousness in these patients, however, some consideration is due to their course during the first six months after discharge from the hospital (Table 5). Five patients died during their initial hospitalization after a period of confusion varying from four to twenty-three days; a sixth, who remained demented for

TABLE 4. Comparison of Durations of Coma or Semicoma and of Confusion.

DURATION OF COMA OR SEMICOMA	ALL CASES	DEATH AFTER 4-23 DAYS*	DURATION OF CONFUSION		
			21 DAYS OR LONGER	10-20 DAYS	3-9 DAYS
Unknown	1	0	1	0	0
Less than 1 hour	10	1	0	6	3
1-5 hours	16	2	6	2	6
6-11 hours	5	1	0	2	2
12-24 hours	5	0	2	2	1
Above 24 hours	2	1	1	0	0
Totals	39	5	10	12	12

spoken and written language, as well as ability to read and write, was disturbed in all cases. In only 4 patients was the disturbance of speech such as to indicate localized cerebral damage, and of these, two had a "jargon dysphasia." The majority of

TABLE 5. Aftereffects of 29 Patients.*

STATUS	NO OF CASES	PERCENTAGE†
Asymptomatic patients	11	38
Patients with symptoms after hospitalization‡	18	62
Headache	11	38
Dizziness	12	41
Weakness and easy fatigability	7	24
Insomnia	1	3
Disturbance of sexual function	1	3
Fear, anxiety and worry	3	10
Patients with neurologic signs after hospitalization‡	9	31
Cranial nerve palsies	4	14
Babinski's sign	4	14
Unsteady gait	3	10
Dysphasia	4	14
Dysarthria	1	3
Patients with epileptiform seizures	2	7
Patients with change in mental status at end of 6 months‡	12	41
Dementia	2	7
Partial intellectual impairment	7	24
Marked personality change	7	24
Ability to work		
Returned to work within 3 months	15	52
Returned to work between 3 and 6 months	4	14
Unable to work at end of 6 months	4	14
Did not work before accident, but capacity estimated to be impaired	3	10
Child (no criteria for adjustment)	1	3

*All patients were followed for at least six months, but the figures do not always represent the findings at the end of that time. The signs and symptoms listed were present for variable periods of time following hospitalization

†There was, of course, some overlapping, some patients having more than one symptom or sign

‡Patients with dementia are not listed with those having marked personality change, but 5 patients with partial intellectual impairment were adjudged to have striking personality disorders as well. We are indebted to the other members of the research group for data on the ultimate follow-up, and particularly to Dr Edwin M. Cole for a report on the intellectual status of the patients

these patients had a disturbance in the understanding of the meaning of sentences that lasted longer than the period of disorientation.

Comparison of the durations of coma or semicoma and mental confusion (Table 4) shows that the relation between the two was not direct.

COURSE AFTER HOSPITALIZATION

Discussion of the late effects of severe injuries to the head is beyond the scope of this paper. In the

more than three months after removal of a subdural hematoma, died after a second exploratory craniotomy. Four patients could not be adequately followed. In 2 cases satisfactory reports concerning the patients were received from other institutions. The remaining 27 patients were examined one or more times in the Head-Injury Clinic of the Boston City Hospital and were followed for at least six months after injury.

A relatively large percentage (38 per cent) of patients remained asymptomatic during the six-month follow-up period. In general, symptoms did not begin after discharge but were existent throughout the post-traumatic course. Sixty-two per cent of patients who were followed had some complaint attributable to their head injury, but in only 2 cases were the symptoms severe. Nine patients had two or more of the symptoms listed in Table 5, whereas 4 presented the classic triad of headache, dizziness and easy fatigability. Headache and dizziness, whenever present, usually lasted for at least two to four months, and in 5 cases each was present for longer than six months. Residual neurologic signs were found in 9 cases (31 per cent), and in most of them persisted in some degree for the entire follow-up period; 2 patients developed epileptiform seizures late in their course. Those patients with marked intellectual impairment a few weeks after injury continued to show the same defect in diminishing degree for at least six months; the incidence of intellectual defect at the end of three and of six months was approximately the same. All 4 cases with dysphasia improved considerably, and at the end of six months it was difficult to demonstrate any defect in 3. Two thirds of the patients who were followed had returned to their usual occupations within six months after injury, and only 14 per cent could be considered completely incapacitated by their head injury at the end of this time.

DISCUSSION

Prolonged confusion resulting from head injury was accompanied by important changes in vital

is in about half the 39 patients, and the duration of such changes did not seem to be significantly related to the duration of confusion. From these observations, it seems safe to conclude that mental confusion in patients with head injuries is not merely the result of respiratory or peripheral circulatory disturbances or elevated body temperature. The evidence, on the other hand, indicates that prolonged confusion is the direct result of severe trauma to the brain, a conclusion supported by the high incidence of findings indicating cerebral damage, such as an abnormal electroencephalogram, bloody spinal fluid under increased pressure, extensor plantar responses and skull fracture. From the data obtained in this small series it is not justifiable to conclude that confusion results from increased pressure, the presence of blood in the spinal fluid or a combination of these. Indeed, we are well aware of many cases in which all these are present without prolonged confusion. No combination of signs, apart from those of the mental disorder consequent on the confused state, was invariably present. From the prognostic standpoint, the presence of convulsions during the hospital course, incoherence, stupor or a temperature over 101°F. was particularly important in this series, and these signs were found only in association with the longest confusion. This evidence also supports the theory that fever in such injuries is of cerebral origin, as indicated by Goldstein.¹⁴ The duration of the period of disorientation was prolonged by advancing age and by alcoholism. Among 190 unselected patients with head injuries previously reported,⁹ 9 per cent were in a state of coma or confusion during the first twenty-four hours. The series studied here, in which coma or confusion persisted for longer than three days, constitutes 8 per cent of a larger but overlapping group. These figures suggest that when confusion is present more than twenty-four hours, it is usually associated with severe cerebral damage and is apt to persist for days or weeks. Although short-lasting disorientation is usually encountered immediately after head injury, this type of disturbance tends to be limited to minutes or hours, and is probably related to alcoholism, to a memory gap or to the emotional factors attendant on loss of consciousness. In this small series it is interesting that euphoria, apathy and apathy were more frequent in the patients in whom the period of confusion was short. It is possible that severe intellectual impairment masks these emotional and personality disturbances, which become more evident when orientation returns.

The order in which the various abnormalities appeared is constant for speechlessness, incoherence and disorientation in place, situation and person. These are milestones in a gradually progressive improvement in cerebral function. There is,

however, a diurnal fluctuation most noticeable in any function for the first few days after its reappearance. In relation to these events in mental awakening, drowsiness and restlessness hold no fixed place, disappearing relatively earlier in the more lengthy confusions. It is possible that they reflect disorder of a different kind, — for example, emotional reaction — for the person with limited consciousness is still capable of such reaction. The duration of abnormality of pulse rate may likewise be related to emotional disturbance as well as to damage to vital centers. Its inconsistency reveals such multiple relations. The motor manifestations, such as inability to speak and extreme restlessness requiring restraint, disappear long before the intellect returns to normal. The duration of the period in which the patient is unable to make any response to simple psychologic tests was found to be a measure of the severity of the confusion, for the duration of such disability was related to the duration of the period of confusion. The first responses were made shortly before normal orientation reappeared.

The cases here reported are included in a larger group investigated by us,⁹ in which the incidence of severe intellectual impairment at the end of three months was about 2 per cent. All the patients in the present series with persisting intellectual defect at the end of three and six months had a period of disorientation in excess of nineteen days, an indication that both these disturbances are aspects of the same essential disorder of cerebral function. The mental phenomena of the confused state can be regarded as the initial deeper stage of what later becomes intellectual impairment. This disturbance is complicated by the influence of age and alcoholism. No cases were encountered of disproportion between the severity of confusion and the degree of residual mental defect of the type mentioned by Symonds.⁶ These patients are being followed for long periods by the other investigators in the project, and our present intention is simply to give an indication of the clear relation between the early confusion and the later disturbances of the intellectual sphere.

The duration of amnesia is closely related to that of confusion. All the patients in this series appeared to have retrograde and post-traumatic amnesia, but reliable estimate of its duration was obtainable only in retrospect after disorientation and other disturbances had entirely cleared. In the early stages of hospitalization, therefore, the duration of confusion (disorientation) is the best criterion for evaluation of the severity of damage to mental function. Unfortunately, such information is often unavailable when patients are seen late in convalescence, and the post-traumatic period of amnesia is then the only basis on which the duration of disturbed consciousness can be estimated. Whereas post-traumatic amnesia appears to coincide fairly well in duration

with disorientation, measurement of the latter would provide more reliable and more easily obtainable objective data.

SUMMARY

In 39 patients with prolonged disturbances of consciousness following head injury, the frequency and duration of abnormal signs were analyzed. A high incidence of abnormal findings, such as an altered electroencephalogram, skull fracture, bloody spinal fluid under increased pressure and Babinski's sign, gave evidence that prolonged mental confusion is associated with severe brain damage. Important changes in vital signs were present in only half the cases and appeared to be independent of the presence and duration of confusion.

During the period of hospitalization immediately following injury, intellectual disturbances outnumbered other mental abnormalities. Emotional disorders tended to appear later than the cognitive dysfunctions, and persisted longer; they were frequent even in cases of short confusion.

Ability to speak returned on an average within the first day. The first response to simple psychologic tests appeared during the second week, before correct orientation in place, situation and time, which returned in that order. Drowsiness and restlessness held no fixed place in the order of recovery, and appear to be independent of the course of recovery of intellectual function.

Gross intellectual defect persisted for six months in 31 per cent of the series, and in every case was preceded by a period of confusion lasting longer than nineteen days.

The duration of disorientation proved to be one of the most reliable and easily obtainable criteria of the seriousness of mental prognosis. The duration of post-traumatic amnesia is directly related to the period of disorientation and thus of equal value, but is available only later and is thus a purely subjective quantity.

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MENINGOCOCCAL MENINGITIS*

A Report of Thirty-Three Cases with No Deaths

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THIRTY-THREE cases of meningococcal meningitis were admitted to the Contagious Disease Service of the Station Hospital at Camp Grant, Illinois, between January 4 and July 3, 1943. During this period, there were 10 additional cases of acute purulent meningitis, with 1 death. No organisms were found either on repeated spinal-fluid examination or on blood culture. Because the etiology of these cases is not clear, they are not included in this discussion.

Four cases are presented in detail, including one that was complicated by hemorrhage into the adrenal glands (Waterhouse-Friderichsen syndrome). All the patients were adults between the ages of eighteen and thirty-four years.

frequently there was an associated cough, sore throat and nasal discharge. The admission temperatures varied from 98 to 104.4°F., with an average

TABLE 1. Frequency of Symptoms.

SYMPTOM	NO. OF CASES	PERCENTAGE
Headache	32	97
Fever	32	97
Vomiting	30	91
Chills	24	73
Sore throat	12	36
Cough	11	33
General aching	8	24
Nasal discharge	6	18

of 100.8°F. Fever persisted on an average of days, with a variation of one to fifteen days.

Physical Signs

A rigid neck was present in all 33 patients, and a positive Kernig sign was elicited in all but one (Table 2). Coma, semicoma or drowsiness occurred frequently. Skin manifestations, usually in the form of petechiae, were not uncommon. Occasional

Symptoms

In most cases the onset was acute, with severe headache, chills, fever and vomiting (Table 1). Less

*From the Medical Service, Station Hospital, Camp Grant, Illinois.

a generalized pink macular or maculopapular rash was seen. Neck rigidity persisted on an average of 6.6 days, with a variation of two to seventeen days.

Laboratory Findings

A total and a differential cell count, a Pandy's test, a sugar determination, a stained smear and a culture on chocolate agar (incubated in an atmos-

TABLE 2. Frequency of Physical Signs.

PHYSICAL SIGN	NO OF CASES	PERCENTAGE
Stiff neck	33	100
Kernig's sign	31	94
Skin manifestations:	20	61
Petechiae alone	13	40
Petechiae and purpura	3	9
Petechiae and maculopapular rash	3	9
Maculopapular rash alone	1	3
Drowsiness	11	33
Coma	9	27
Delirium	3	9

phere containing 10 per cent carbon dioxide) were routinely performed on all spinal fluids. In all but 1 case, the diagnosis of meningococcal meningitis was confirmed by the presence of the characteristic gram-negative intracellular diplococci in the smear of the spinal fluid or by their isolation in culture. In the remaining case, which presented the typical clinical and laboratory findings of an acute meningitis, the organisms could be isolated only in blood culture. On initial examination the spinal fluid was frankly purulent in all but 2 patients. The first lumbar puncture in these cases revealed a clear, colorless fluid containing only a few lymphocytes, but a tap repeated several hours later revealed the presence of many polymorphonuclear leukocytes.

Eighteen of the 33 patients had spinal-fluid cell counts of 5000 to 20,000, with 74 to 100 per cent polymorphonuclear leukocytes (Table 3). The

TABLE 3. Cell Counts of the Initial Spinal Fluids.

WHITE-CELL COUNT	NO OF CASES	PERCENTAGE
Less than 1,000	3	9
1,000-4,000	8	24
5,000-9,000	9	27
10,000-19,000	9	27
20,000-39,000	3	9
40,000-59,000	1	3

organism was seen in the spinal-fluid smear in 27 cases (82 per cent). Spinal-fluid culture was positive in 26 cases (80 per cent). Group 1 meningococci were found in all cultures that could be successfully typed (21 cases). In only 17 cases (51 per cent) was the spinal-fluid sugar decreased. Eleven patients (33 per cent) had a positive blood culture. The white-cell count of the blood in most cases varied between 15,000 and 25,000, with a moderate to marked polymorphonuclear leukocytosis.

Treatment

Treatment in almost all cases was begun in twenty-four hours or less after the onset of symptoms. Sulfadiazine, sulfathiazole and polyvalent antimeningococcus serum were used singly or in

combination. The way in which these therapeutic agents were employed is summarized in Table 4.

When sulfathiazole and sulfadiazine were used in combination, intravenous sodium sulfathiazole was the drug employed to initiate treatment. This was followed by oral sulfadiazine as soon as the patient was able to take medication by mouth. When sulfadiazine was used exclusively, the sodium salt of sulfadiazine was substituted for the sodium sulfathiazole, which was used only when sodium sulfadiazine was not available, the latter drug being preferred because of its lower toxicity. In general, treatment was initiated by giving intravenously 5 gm. of sodium sulfadiazine or sodium sulfathiazole dissolved in 100 cc. of distilled water. If oral sulfadiazine could not be given within twelve hours after the onset of treatment, the intravenous administration of sulfonamide was repeated. As a rule it was unnecessary to repeat the parenteral injection more than once, since at the expiration of twenty-four hours the patient was usually able

TABLE 4. Type of Treatment.

THERAPEUTIC AGENT OR AGENTS	NO OF CASES	PERCENTAGE
Sulfadiazine alone	14	43
Sulfadiazine and sulfathiazole	14	43
Sulfadiazine and serum	2	6
Sulfadiazine, sulfathiazole and serum ..	3	9

to take sulfadiazine by mouth. When oral therapy was begun, 1 or 2 gm. of sulfadiazine was given every four hours, the larger dose usually being employed for only twenty-four to forty-eight hours, depending on the blood level of the drug. Thereafter, sulfadiazine was continued in doses of 1 gm. every four hours until the patient was afebrile for one week, whereupon therapy was abruptly discontinued. Since most patients were afebrile after the fifth day, the average case received sulfadiazine for eleven or twelve days.

The dosage of sulfadiazine was governed to some extent by the blood level of the drug. An attempt was made to obtain a blood-sulfadiazine level of 8 to 12 mg. of the free drug per 100 cc., preferably by the second day of treatment. When the blood level was much below 8 mg., however, no attempt was made to increase the blood level by giving larger than the usually recommended doses of sulfadiazine if the patient seemed to be making satisfactory progress. In Table 5 are given the blood and spinal-fluid sulfadiazine levels of 14 patients who received sulfadiazine exclusively.

The twenty-four-hour fluid intake and urinary output were measured for all patients receiving sulfonamide therapy. This was considered to be of the utmost importance. A urinary output of not less than 1500 cc. every twenty-four hours was desired. If it was less than this, fluids were forced by mouth or intravenously to prevent anuria.

Polyvalent antimeningococcus serum was used in conjunction with a sulfonamide drug in 5 cases.

Its use was reserved for markedly fulminating cases and for those that seemed to be responding poorly to sulfonamide therapy. Despite negative intradermal and intraocular tests in all cases, a reaction to the serum was encountered in 2 patients, chills and headache occurring during administration — apparently an anaphylactic reaction. In the remaining 3 cases, serum therapy was followed one week later by urticaria and arthralgia.

Routine spinal-fluid drainage was not performed. All patients received a minimum of two lumbar

Complications

A serious complication was encountered in only 1 case, this consisting of a probable hemorrhage into the adrenal glands (Waterhouse-Friderichsen syndrome¹⁻³). This case is presented in detail below. Another patient, who had apparently made a satisfactory recovery, returned two months after discharge with the signs and symptoms of a chronic meningoencephalitis of unknown etiology. A third patient, who had made an uneventful recovery, was discovered to have an unrelated active, minima

TABLE 5. Blood and Spinal-Fluid Sulfadiazine Levels of Patients Treated with Sulfadiazine Only.

CASE No.	DAY OF TREATMENT									
	2ND mg./100 cc.	3RD mg./100 cc.	4TH mg./100 cc.	5TH mg./100 cc.	6TH mg./100 cc.	7TH mg./100 cc.	8TH mg./100 cc.	9TH mg./100 cc.	10TH mg./100 cc.	
1	2.52		10.1		8.0					
2	7.3	(1.1) 1.3	4.6 (7.15)		8.7		10.1		8.4	
3	7.4	(9.6) 10.5	7.15				11.0			
4	8.2	7.7				8.9			9.7	
5		6.4 (4.96)		11.0		8.69				
6	8.8	7.15	7.85		8.99		11.6			
7	2.32			11.6				7.51		
8	6.3 (8.0)	6.6	4.8			7.7				
9	9.7	12.9	7.7			6.4				
10	4.8	6.3		9.7						
11	9.2		7.63				8.4			
12	(3.6)	6.4		9.7			10.5			
13	5.3	8.1				7.0				
14		5.2		9.2					10.9	

*The spinal-fluid levels are given in parentheses.

punctures — one for diagnosis and the other for checkup before discharge from the hospital. Indications for additional lumbar punctures were persistent, severe headache, frequent vomiting and a slow or doubtful clinical response to therapy. In the last instance, repeated spinal-fluid examination was required so that the progress of the patient could be followed more closely.

Morphine sulfate in doses of $\frac{1}{6}$ or $\frac{1}{4}$ gr. was found to be the drug of choice for the control of headache and restlessness. In delirium, however, this drug was found to be of little or no value. In a wildly excited patient with true delirium, intravenous Pentothal Sodium was used, with gratifying success. Pentothal Sodium employed in this manner has the disadvantage of an extremely short-lived effect. This difficulty was overcome by slow, continuous administration, made possible by diluting the drug with a large quantity of normal saline solution. A total of 1 gm. of Pentothal Sodium was employed. To quiet the patient approximately one fourth of this amount, or 0.25 gm., was given intravenously as a 2.5 per cent solution in distilled water. The remainder, or 0.75 gm., was added to 1000 cc. of normal saline solution and given intravenously at a rate that just kept the patient from restlessness. The administration of this solution required about six hours. Repetition of the drug was unnecessary. The usual precautions for its administration were observed, and a trained attendant was constantly present.

case of pulmonary tuberculosis. The remaining complications were minor and transient. Eleven patients (33 per cent) developed herpes simplex and 2 (6 per cent) had a transient diplopia.

CASE REPORTS

The first two cases present the usual picture of an uncomplicated acute meningococcal meningitis.

CASE 1. G. H., a 19-year-old soldier, was admitted to the hospital complaining of headache, vomiting and chills that had begun a few hours previously. The past medical history and the family history were noncontributory.

Physical examination revealed a well-developed, well-nourished, conscious but stuporous man. The temperature was 104°F., the pulse 120, and the respirations 20. Neck rigidity was marked. Kernig's sign was positive, and the deep tendon reflexes were normally active. The skin was clear. A lumbar puncture revealed a cloudy spinal fluid containing 8530 white cells per cubic millimeter, of which 96 per cent were polymorphonuclear leukocytes and 4 per cent lymphocytes. The spinal-fluid smear showed an occasional pair of gram-negative extracellular diplococci. Spinal-fluid culture was positive for Group 1 meningococci. A blood culture was negative. The blood white-cell count was 20,100 with 95 per cent polymorphonuclear leukocytes and 5 per cent lymphocytes.

The patient was given 5 gm. of sodium sulfadiazine in 100 cc. of distilled water intravenously and 4 gm. of sulfadiazine by mouth, and 1 gm. of sulfadiazine thereafter every 4 hours for 11 days.

Recovery was uneventful, all clinical signs of meningitis disappearing by the 5th hospital day. The only complication was the development on the 11th day of a drug rash and fever, which quickly subsided when the sulfadiazine was discontinued.

CASE 2. G. M., a 29-year-old soldier, had been well until 1 day prior to admission, when he developed severe headache,

ness of the neck, chills and vomiting. The past medical history and the family history were negative.

Physical examination revealed a conscious but drowsy man whose temperature was 104.2°F, the pulse 112, and the respirations 24. The skin was clear. The pharynx was slightly injected. Neck rigidity was marked. Kernig's and Brudzinski's signs were markedly positive. A lumbar puncture revealed a cloudy spinal fluid containing 22,470 white cells per cubic millimeter, of which 94 per cent were polymorphonuclear leukocytes. The globulin was markedly increased. The spinal fluid sugar level was 4.2 mg per 100 cc. Smear showed gram negative intracellular diplococci and culture of this fluid yielded Group I meningococci. A blood culture was negative. The blood white cell count was 14,400 with 74 per cent polymorphonuclear leukocytes and 20 per cent lymphocytes.

The patient was given 5 gm of sodium sulfathiazole in 30 cc of distilled water intravenously and 2 gm of sulfadiazine by mouth followed by 1 gm every 4 hours. On the 3d day, because of apparent failure to improve clinically and low blood sulfanamide level — 2.12 mg per 100 cc — 1 gm of sulfadiazine was given by mouth, followed by 2 gm every 4 hours for the next 7 days. By the 8th day of treatment the blood sulfadiazine level had reached 10.3 mg per 100 cc. Thereafter the patient received 1 gm of oral sulfadiazine every 4 hours until the 11th day, when therapy was discontinued. The only reaction possibly attributable to sulfadiazine was a transient microscopic hematuria. Recovery was uneventful. All clinical signs of meningitis having disappeared by the 7th hospital day.

The next case was probably complicated by hemorrhage into the adrenal glands.

CASE 3. J. B., a 23-year-old soldier, was admitted to the hospital with a chief complaint of headache. He had been ill until 2 days prior to admission, when he developed a sore throat and a slight cough. A few hours before admission he began having severe headache, chills, fever and vomiting. Physical examination revealed an acutely ill man who was conscious but drowsy. The temperature was 103.2°F, the pulse 136, and the respirations 26. There were numerous petechiae and many areas of marked purpura over the trunk and extremities. There were also a few purpuric spots over the soft palate and a small hemorrhage beneath the left alar conjunctiva. The pharynx was moderately inflamed. Neck rigidity was marked. The Kernig and Brudzinski signs were positive. The deep tendon reflexes were normally active. The heart sounds were of fair quality. The blood pressure was 70/45. A lumbar puncture revealed cloudy spinal fluid under slightly increased pressure. The white cell count was 775 with 77 per cent polymorphonuclear leukocytes and 22 per cent lymphocytes. The globulin was markedly increased and the sugar level was 55.5 mg per 100 cc. A smear showed numerous gram negative intracellular diplococci. Cultures of the fluid and the blood were both positive for Group I meningococci. The blood white cell count was 11,000 with 95 per cent polymorphonuclear leukocytes and 5 per cent lymphocytes.

The patient was given 5 gm of sodium sulfadiazine intravenously, followed by 1 gm of oral sulfadiazine every 4 hours. A few hours after treatment was begun, he lapsed into a restless coma. There was slight cyanosis, the pulse became irritable, and the blood pressure could not be obtained. Unlike the usual picture of shock, the veins were full and the extremities were warm and moist. The blood chloride level was 216 mg per 100 cc, and the blood sugar level 97 mg. Because of the clinical picture resembling shock, the blood chloride level and the striking purpura it was thought that a hemorrhage into the adrenal glands had occurred. Accordingly the patient was given large quantities of normal saline solution intravenously, adrenocortical extract intravenously and intramuscularly, a 500-cc blood transfusion and oxygen intranasally. Within 3 hours the blood pressure had risen to 70/55. Several hours later the

patient regained consciousness. The blood chloride level several days after this acute episode was 472 mg per 100 cc.

Further treatment with sulfadiazine and intravenous polyvalent antimeningococcus serum brought about a slow but uneventful recovery.

The last case, one of unusual interest, is presented to show that meningococcal meningitis cannot be ruled out on the basis of a single negative spinal-fluid examination. It further serves to illustrate how quickly the spinal fluid picture can change.

CASE 4. E. A., a 28-year-old soldier, was admitted to the hospital complaining of headache, chills, general aching, sore throat and vomiting that had begun several hours before.

Physical examination presented an acutely ill patient who was conscious but drowsy. The temperature was 100.8°F, the pulse 100 and the respirations 20. There were a few widely scattered petechiae over the trunk and extremities. The pharynx was moderately injected. The neck was slightly rigid and Kernig's sign was positive. The deep tendon reflexes were sluggish. A lumbar puncture revealed clear colorless spinal fluid under normal pressure. It contained only 6 cells per cubic millimeter, all of which were lymphocytes. No organisms were seen on smear. The globulin was not increased and the sugar level was 83 mg per 100 cc. The blood white cell count was 46,650 with 91 per cent polymorphonuclear leukocytes.

The patient was treated symptomatically. Within a few hours the number of petechiae had increased, the neck became more rigid and Kernig's sign was more markedly positive. Five hours after the first spinal fluid examination a lumbar puncture was repeated. At that time the spinal fluid was cloudy and under increased pressure and showed a cell count of 7450 with 92 per cent polymorphonuclear leukocytes and 5 per cent lymphocytes. The globulin was markedly increased, the sugar level was 46.5 mg per 100 cc and a smear showed numerous gram negative intracellular diplococci. Culture of the spinal fluids from the two lumbar punctures showed Group I meningococci. The blood culture was also positive for meningococci.

Following treatment with intravenous sodium sulfathiazole and oral sulfadiazine the patient made an uneventful recovery.

SUMMARY

The symptoms, physical signs, laboratory findings and treatment of 33 cases of meningococcal meningitis are presented.

The therapeutic agents employed were sulfadiazine, sulfathiazole and polyvalent antimeningococcus serum.

In this unselected series of cases there were no deaths.

Only one serious complication was encountered — an apparent hemorrhage into the adrenal glands (Waterhouse-Friderichsen syndrome).

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MEDICAL PROGRESS

INHALATION THERAPY*

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INHALATION therapy may be defined as the administration of gases through the respiratory system for the treatment of various types of anoxia or of oxygen want of the tissues. The indications and value of oxygen therapy have been reported by Boothby and his associates, Barach and his associates and others. The principal use of oxygen is to relieve the anoxia that occurs in a wide variety of disturbances of the circulatory, respiratory and central nervous systems, in preoperative and post-operative conditions and in military medicine. Such therapy has had an amazing growth.

Other therapeutic gases, agents and methods of maintaining respiratory function have been developed. Inhalations of carbon dioxide, helium-and-oxygen mixtures, of water-vapor and of nebulized sprays of various therapeutic agents, repeated bronchial relaxation therapy, the addition of positive pressure with oxygen or helium-and-oxygen mixtures and continuous pulmonary-arrest therapy have been increasingly employed, with successful results. It is beyond the scope of this report to review the many papers that have been written on these subjects. Only those that appear to be especially significant will be considered.

EQUIPMENT

Excellent reviews of the various types of equipment may be found in papers by Boothby and his associates,¹⁻⁵ Eckman and Barach⁶⁻¹⁰ and Ellis¹¹ and in a small manual recently published by Andrews.¹² The more frequently used methods for administering oxygen are the nasal or nasopharyngeal catheter, face masks and tents and the various types of enclosing tents. Each method has its special advantages and disadvantages. With the above methods, oxygen can be given in 40 to 70 per cent concentrations.

The development of the B.L.B. apparatus in 1938 and its later modifications^{13, 14} make it possible to administer concentrations of oxygen close to 100 per cent. This is partially a rebreathing type of apparatus and can be used for helium-and-oxygen and carbon dioxide therapy. Barach and Eckman^{6, 7} in a careful analysis reported the disadvantages of the B.L.B. apparatus — namely, the accumulation of carbon dioxide and the development of negative

and positive pressures within the mask at low flow of oxygen owing to the resistance of the sponge rubber valves. These disadvantages can be largely corrected by using high flows of oxygen. A critical discussion and analysis of the B.L.B. apparatus with determinations of the percentages of alveolar air and carbon dioxide at various flows of oxygen and comparison with the Christie and Haldan masks, appeared in the English literature in a paper by Card et al.¹⁵

In a recent paper Barach and Molomut¹⁶ describe a new modification of the Barach-Eckman apparatus. This mask is a distinct credit to the ingenuity of the authors and is of tremendous practical value. An air injector is utilized to provide accurately controlled percentages of oxygen in the inspired air. By means of an expiratory valve on the face mask, which is a comfortable one, and an inspiratory valve at the entrance to the collecting bag, rebreathing is eliminated. Accumulation of carbon dioxide and mechanical resistance to respiration are greatly reduced with this arrangement of valves. A soft latex-rubber collecting bag of 1000-cc capacity makes it possible for the patient to breathe deeply with comfort. In addition the face mask has an attached expiratory outlet that has been metered for positive pressure in expiration up to 4 cm. of water pressure. A higher positive pressure develops during dyspnea when the 4-cm. orifice is used. The apparatus can be used to deliver 40 to 95 per cent oxygen or helium-and-oxygen mixtures, with or without positive pressure. If carbon dioxide therapy is prescribed, the inspiratory valve may be removed to allow rebreathing. I^{17, 18} have used this apparatus in various types of cardiorespiratory disease and find it practical and economical. Cowart and Mitchell¹⁹ made a critical analysis of the mask and attest to its improved functional value. Epstein²⁰ compared the pressure changes taking place in the nasal piece of this apparatus with those in the nasal piece of a standard B.L.B. mask. He confirmed the previous observations by Barach and Eckman that the pressure changes during inspiration and expiration are considerably smaller with the injector apparatus than with the B.L.B. mask. When using higher concentrations of oxygen with the B.L.B. mask he observed an increasing rise of pressure against expiration. The variations in pressure in the meter mask were found to be the same at all flows and less in all cases than in the B.L.B. mask.

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The helium-and-oxygen hood rebreathing apparatus^{9, 10} is the most effective one for giving oxygen or helium-and-oxygen mixtures, with or without positive pressures. The percentage concentrations of the mixtures can be exactly controlled. Positive pressures up to 6 cm. of water can be applied to the inner surface of the lung during both inspiration and expiration. The apparatus consists of a gas-tight rotor blower, two canisters for the carbon dioxide absorber, a rheostat to determine the volume of air flow and its temperature, tubal connections, an ice-containing cabinet and a plastocele hood in which the patient's head lies, with closure effected by a soft-rubber collar. In this rebreathing circuit only the oxygen is used up when enclosed. Cooling, dehumidification and removal of carbon dioxide can be efficiently carried out. The apparatus is widely employed in the treatment of severe bronchial asthma, various types of pulmonary edema and obstructive dyspnea.

A new apparatus for administering oxygen is described by Bortin.²¹ The exhaled air passes through a carbon dioxide absorber and thence into a reservoir bag. When the bag is sufficiently inflated, the purified air returns to the patient. The automaticity depends on an ingenious series of valves. This is an economical method of giving oxygen, since little, if any, of the gas is wasted. It appears to have a real value in aviation, where conservation of weight and space is important. Alveolar concentrations of oxygen and carbon dioxide at varying rates of flow have not yet been reported with this apparatus. The many mechanical factors necessary for maintenance, however, probably preclude its general use.

A new apparatus for the administration of helium-and-oxygen mixtures is described by Brubach, Crisp and Neal.²² Separate tanks of helium and oxygen are used, and safety devices regulate the flow of the two gases in accordance with the patient's needs. A safety valve prevents the flow of helium until the oxygen is turned on. An adjustable weight arrangement makes possible the maintenance of a positive pressure in the facepiece. This apparatus permits a wide selection of the percentages of the gases, and when set for 20 per cent oxygen the latter cannot fall more than a fraction of 1 per cent. It is a seemingly foolproof device if all goes well and attention is paid to the many functioning parts: valves, bellows, manometers, weights, flow meter and so forth. Any desirable combination of helium and oxygen, with or without positive pressure, however, can be given with safety and relative inexpensiveness with the most ideal apparatus — the Barach-Eckman-Molomut mask apparatus,¹⁰ previously described.

An equalizing pressure chamber for immobilizing the lungs by air pressure is described by Barach.²³⁻²⁶ The total pressures on both sides of the diaphragm are made equal. Under these circumstances adequate ventilation of the lungs is accomplished with-

out voluntary breathing and without discernible movement of the ribs and diaphragm. Four out of five patients with advanced pulmonary tuberculosis considered unsuitable for any type of collapse therapy showed a consistent response to equalizing-pressure therapy — namely, a marked gain in weight, a decrease in cough and sputum, a fall in the sedimentation rate and the temperature to normal, definite clearing of shadows on the x-ray film, including cavities, and subjective improvement. This form of therapy, although at present impractical on a large scale, shows promise for the candidate for pneumothorax or thoracoplasty with advanced pulmonary tuberculosis.

CARBON DIOXIDE THERAPY

The principal use of carbon dioxide therapy is to stimulate the respiratory center. An increase in the respiratory rate and in the depth of respirations characterizes effective therapy of this type. Carbon dioxide probably acts by increasing the acidity of the respiratory center. Increase in the acidity of the blood flowing through the carotid body and low oxygen pressures in the carotid body also stimulate breathing. In addition, carbon dioxide shifts the oxygen-dissociation curve to the right and dilates the cerebral vessels.

Physiologic Effects

In seeking to understand the rationale of carbon dioxide administration, it is well to recall that Gibbs, Gibbs and Lennox²⁷ demonstrated a selective increase in cerebral flow by an increased carbon dioxide tension. Behnke, Forbes and Motley²⁸ similarly observed an increase of 33 per cent in the diameter of the pial vessels of the cat as a result of increasing the pulmonary, carbon dioxide tension. Shaw, Behnke and Messer²⁹ also believe that, apart from the shift of the oxygen-dissociation curve to the right with high carbon dioxide tensions, increased cerebral circulation accompanying carbon dioxide inhalations in part explains the increased effectiveness of a given pulmonary oxygen tension. The supply of blood to the vital centers is augmented by the cerebral vasodilatation. The above observations offer a partial explanation of the ability of increased pulmonary carbon dioxide tension to improve the effectiveness of oxygen on the central nervous system.

Gellhorn³⁰ demonstrated that the anoxia and circulatory collapse observed in human subjects when breathing atmospheres of only 8.5 per cent oxygen could be prevented by adding 3 per cent carbon dioxide to the atmospheres breathed. He attributed this to the action of carbon dioxide in increasing the respiratory volume, venous return and cerebral blood flow, stimulating the respiratory center and shifting the oxygen-dissociation curve so that the supply of oxygen to the tissues is augmented. The anesthetist thus has a simple physi-

ologic method for increasing cerebral blood flow with mixtures of carbon dioxide and oxygen, although this is not necessary if the oxygen concentration of the anesthetic mixture is kept above 20 per cent.

It is important to know when carbon dioxide ceases to stimulate and acts as a narcotic. Brown³¹ demonstrated that the therapeutic effect depends on whether the action is stimulating or narcotic. He showed that the respiratory minute volume in healthy men was increased 279 per cent by a 10.4 per cent concentration of carbon dioxide in the inspired air, although at concentrations above 7.5 per cent the increase was negligible. Above 10.4 per cent, a decrease in minute volume from the maximum began.

The efficacy of carbon dioxide in carbon monoxide poisoning is due not merely to stimulation of respiration but, as Stadie and Martin³² point out, to the displacement of carbon monoxide by carbon dioxide. Small concentrations of carbon dioxide (1 to 2 per cent) in the presence of 50 per cent oxygen may also enhance the effectiveness of oxygen by increasing its movement from the blood to the tissues (Bohr effect).

Therapeutic Uses

Carbon dioxide-and-oxygen therapy has been reported to be of value during and after anesthesia, in the treatment of various asphyxias, electric shock, drowning, morphine poisoning, atelectasis neonatorum, postoperative atelectasis, epilepsy and dementia praecox and as an expectorant. The B.L.B. or Barach meter mask may be used, employing concentrations of 3 to 10 per cent carbon dioxide in oxygen.

Henderson and his associates³³⁻⁴⁷ first emphasized the value of carbon dioxide in depressed respiratory states, particularly those due to carbon monoxide poisoning. They⁴⁸⁻⁵³ extended its use to cardio-respiratory lesions characterized by dyspnea. Barach⁵⁴ decried this extended usage and proved its physiologic unsoundness. Other investigators questioned its value in asphyxia and atelectasis. Eastman, Dunr and Kreiselman⁵⁵ made a study of the relative value of pure oxygen and of carbon dioxide mixtures in experimental resuscitation. Their work showed that oxygen is of the greatest importance in the treatment of asphyxia in dogs and that the effect of giving carbon dioxide in this condition is actually harmful. They concluded that the indiscriminate use of carbon dioxide should be guarded against in the resuscitation of the asphyxiated. Increasing evidence⁵⁶ favors the use of oxygen or helium-and-oxygen mixtures, with and without positive pressure, in the management of various types of atelectasis. He thought that the increased respiratory effort produced by carbon dioxide would be harmful with an obstructive respiratory picture, since it tended to increase the

intrathoracic negative pressure, thus producing pulmonary edema. This could be prevented by using oxygen or helium-and-oxygen mixtures, particularly with positive pressure. Martinez⁵⁷ also prefers pure oxygen to oxygen and carbon dioxide. He employed a pulmotor in a series of 500 infants and believed it to be the most effective method of resuscitating babies.

The Council on Pharmacy and Chemistry,⁵⁸ in an excellent review of the status of oxygen-and-carbon dioxide therapy, states that, since there has been no adequate evidence of a state of carbon dioxide deficiency of sufficient severity or frequency in clinical disease, the value of such therapy cannot be explained on a deficiency basis. Furthermore, no adequate evidence has yet been presented proving the value of such mixtures in the routine therapy of pneumonia or heart disease.

Considerable controversy still exists concerning the over-all value of carbon dioxide inhalation as an expectorant in pulmonary disease. Alison⁵⁹ used inhalations of 5 per cent carbon dioxide with oxygen in some cases of beginning pneumonia and bronchitis in children. He thought that the disease process was aborted through the removal of the mechanical blocking of the airways. Banyai⁶⁰ used inhalations of 10 per cent carbon dioxide in oxygen in cases of pulmonary tuberculosis. He observed that the increase in respiratory rate was followed by easier expectoration and a decrease of cough. Large amounts of sputum were raised by almost effortless expectoration. The sputum changed from a heavy, thick and tenacious type to a thin, serous and watery form. Banyai and Cadden⁶¹ more recently confirmed the value of carbon dioxide inhalation as an expectorant in pulmonary tuberculosis. They attribute its effectiveness to a powerful respiratory stimulating effect, which reflects itself in a stretching and dilatation of the bronchial tubes, powerful peristaltic movements of the bronchi and liquefaction of the exudate that stagnates in the bronchial tree. They stress its contraindication in recent pulmonary hemorrhage, in severe emphysema, in extensive pulmonary fibrosis without atelectasis, bronchiectasis or mucopurulent retention in the air passages, in acute plastic pleurisy and pleurisy with effusion and in hypertension. Campbell and Poulton⁶² encouraged the use of carbon dioxide and oxygen in the treatment of pneumonia.

Basch, Holinger and Poncher^{63, 64} made an exhaustively careful study of the physical and chemical properties of sputum, particularly the influence of drugs, steam, carbon dioxide and oxygen. They concluded that inhalations of steam are more effective than drugs in liquefying sputum. Inhalation of carbon dioxide serves as a most efficient expectorant. Such inhalations reduce the amount of sputum within the bronchial tree by stimulating resorption and render the remainder liquid, so that it is easily coughed up. They found the most efficient regimen

o be a combination of carbon dioxide, steam and expectorant drugs. The above observations of Allison, Banyai, Campbell and Poulton, and Basch et al. certainly favor the use of carbon dioxide inhalation as an expectorant. Nevertheless, one should use it only with a full appreciation of its contraindications as described previously by Basch et al., Eastman et al., Kane, Barach and others.

Barach⁶⁵ employs 5 to 15 per cent concentrations or the management of hiccoughs with considerable success. With higher concentrations the patient becomes drowsy and profoundly relaxed. He generally begins treatment with a 5 per cent concentration and increases it to 15 per cent for three to ten minutes at each treatment if the patient becomes refractory to the lower percentages.

Kornmüller⁶⁶ investigated the influence of 3 to 5 per cent carbon dioxide in oxygen inhalations on the electroencephalographic changes in patients with epilepsy or dementia praecox. The observations demonstrated that carbon dioxide may counteract these changes. He concluded that therapeutic effects may be expected from the use of carbon dioxide in these diseases and that the effects of tetrazol, insulin and electric-shock treatments may be partly due to the fact that they increase the carbon dioxide content of the brain and blood.

At altitudes above 35,000 feet the arterial saturation with oxygen falls rapidly, with associated symptoms of anoxemia, in spite of breathing pure oxygen. Here has been considerable discussion whether the addition of carbon dioxide to the inspired air physiologically increases altitude tolerance in the aviator. Theoretically this is possible on the basis of its ability to increase the dissociation of oxyhemoglobin, to cause cerebral vasodilatation and to stimulate respiratory activity. Gibbs et al.⁶⁷ made a study of arterial and jugular blood and of brain function in normal men who breathed mixtures containing various percentages of oxygen and varying ratios of nitrogen and carbon dioxide. The addition of carbon dioxide to low-oxygen mixtures permitted maximal utilization of the available oxygen and the maintenance of normal brain function as seen in the electroencephalogram. Johnson et al.⁶⁸ studied the effects in dogs of adding carbon dioxide to oxygen-enriched atmospheres in low-pressure chambers. The addition of carbon dioxide corresponding to a tension of 14.3 mm. of mercury increased the minute ventilation by 39 per cent without any beneficial influence on the oxygen tension of the mixed venous blood. The authors concluded that such an added burden should be avoided in human beings when no benefit from carbon dioxide inhalations can be demonstrated.

WATER-VAPOR THERAPY

The principal value of water-vapor therapy is in the treatment of respiratory disease in which thick, tenacious mucopurulent secretions accumulate in the tracheobronchial tree and larynx. Thinner

tions may result from the high humidity of the inspired air, which reduces the loss of water from the mucosa, and expectoration is thus facilitated. Such therapy may be of life-saving value in croup, obstructive dyspneas and inhalation gas poisoning. Everyone is acquainted with the ancient steam kettle and the assortment of croup tents. More modern methods comprise the high-humidity room, humidified mask therapy and the humidified oxygen tent. The minimal allowable relative humidity is 75 per cent. This may be raised to the saturation point in the high-humidity room.⁶⁹ The Walton mechanical humidifier is an instrument that blows water vapor and fine droplets into the air by a fan and centrifugal force. No heat is evolved.

Holinger,⁷⁰ in discussing the therapy of acute laryngotracheal bronchitis, favors placing the patient in a room supersaturated with warm water vapor, the relative humidity reaching 90 per cent if possible. He also mentions briefly the use of oxygen, helium-and-oxygen mixtures, bronchoscopy, tracheotomy and the sulfonamides. No precise technic is described. His results appear good, but more data are necessary for proper evaluation.

It is doubtful whether tincture of benzoin employed in the simple steam humidifiers is of any value. Many believe it to be irritating. Following the suggestion of Healey,⁷¹ I have employed a mixture of menthol, camphor and eucalyptol in a milk-of-magnesia base. Such a mixture was objectively comfortable in a group of patients with inhalation gas poisoning and obstructive respiratory disease.⁷²

In employing oxygen therapy it is essential to ensure adequate water vapor. If one uses the catheter method, it is well to employ a simple water-bottle humidifier. Many prefer a diffusion-head inlet and a water-trap outlet type of humidifier. With the B.L.B. apparatus humidification may be desirable if high oxygen flows are used. Adequate water-vapor concentrations can be obtained with the use of the injector when employing the Barach-Eckman-Molomut mask. If higher humidity is desired, the injector may be removed and the water-bottle type of humidifier substituted. In using the oxygen tent it is difficult to maintain high humidity because the cooling system reduces the humidity. A moderate increase in humidity may be obtained by decreasing the temperature and increasing the circulation to maintain cooling. Davison⁷³ devised a method of connecting a Walton or Gilbert humidifier to the tent canopy, which is most effective, although not sparkproof. A sparkproof humidifier must be employed for use in high oxygen concentrations. This type of arrangement will probably be standard in the tent of the future.

ADMINISTRATION OF VAPORIZED SOLUTIONS

Bronchodilator and Vasoconstrictor Drugs

To the growing list of directive terms must be

system in terms of cargo, crew and ships, the oxygen diffusion gradient from the lungs to the tissue cells being represented by the flow of water from the Great Lakes to the sea.

General Clinical Use

It is of interest at this point to recall that Beddoes in 1795 was enthusiastic about oxygen as a universal panacea. Gradually, however, its use became discredited owing to lack of effective administration and understanding of the principles underlying its use. The employment of 40 to 50 per cent concentrations of oxygen in the treatment of war-gas poisoning and the resultant pulmonary edema again stimulated the application of oxygen therapy to clinical disease.

Various concentrations of oxygen have been successfully employed in pneumonia, pulmonary atelectasis, pulmonary fibrosis, emphysema, bronchial asthma, pulmonary embolism, pulmonary edema of varied etiology, asphyxia and resuscitation, anesthesia, altitude and compression work, circulatory failure, angina pectoris,¹¹² coronary thrombosis,¹¹³⁻¹¹⁵ anemias, abdominal distention,^{1, 116-118} peritonitis, anaerobic infections¹⁰¹ and migraine headaches¹¹⁹; following encephalography^{1, 120}; during fever therapy¹²¹; for peripheral vascular disease, shock of all origin and severe burns; preoperatively and postoperatively; in neurosurgery, obstetrics and traumatic and military surgery; and for a variety of miscellaneous diseases. Reviews of the value of oxygen inhalations in the therapy of cardiorespiratory disease may be found in reports by Barach.^{54, 103, 104, 107, 110} Reviews of the general use of oxygen therapy are given in the reports by Boothby and his associates.^{4, 13}

It is generally appreciated that the onset of anoxemia in a normal person occurs at an altitude of 10,000 to 11,000 feet. At such altitudes oxygen must be supplied. At altitudes above 30,000 feet the effect of lowered barometric pressure is added to that of oxygen want. This results in aeroembolism or aeroemphysema. This is essentially the same as the so-called "bends," or caisson disease, and the air emboli may lodge in any of the blood vessels of the brain, coronary vessels or other terminal vessels. The emboli are nitrogen bubbles released at low pressures, and nitrogen can be partially replaced by oxygen. Preflight oxygen breathing and the same continued throughout ascent and descent prevents these reactions. Flying per se has no effect on the cardiovascular system. The effects noted — electrocardiographic changes and so forth — are all due to the low oxygen or low barometric pressure at high altitudes and the mechanical effects of speed. The latter result from centrifugal force, and the pilot "sees black" in positive accelerations — cerebral anemia and splanchnic and extremity engorgement — and "sees red" in negative accelerations.

Mechanical devices may prevent or cure the latter, and oxygen the former.

Lovelace¹²² in a timely discussion stresses the fact that any clinical condition that causes anoxia is poorly tolerated at high altitudes. He describes the need for adequate oxygen and the difficulty of providing it in cases of concussion of the brain with and without skull fracture, in anemias and fulminating infections and in patients receiving sulfonamide drugs. He stresses the danger of expansion of gas in patients undergoing pneumothorax and in those with penetrating abdominal lesions at high altitudes, due to the lowered atmospheric pressure. In the latter cases the advisability of abdominal decompression with Wangensteen suction is suggested.

It is not enough to administer oxygen of the proper concentration to the anoxic patient. The entire transportation system must be analyzed and the deficiency corrected. Removal and treatment of the cause, supplemental shock therapy and restoration of blood plasma and hemoglobin may be just as important.

High Concentrations

Toxicity. Considerable controversy still exists as to the effects of high concentrations of oxygen on the epithelium of the lung. The earlier observations in animal experimentations demonstrated specific untoward effects generally characterized by pulmonary irritation, convulsions and a decreased metabolism (Barach,¹²³ Binger, Faulkner and Moore,¹²⁴ Smith et al.,¹²⁵ Shilling and Adams,¹²⁶ Behnke et al.¹²⁷ and Campbell^{128, 129}). It is now generally realized, however, that animals are more susceptible to oxygen poisoning than are human beings. Symptoms of oxygen toxicity were reported in normal persons rather than in patients with severe anoxia.

Occasional reports on toxicity in normal and sick persons appeared in the recent literature. Behnke and his associates^{130, 131} observed impairment of neuromuscular control and convulsions in normal subjects exposed to pure oxygen at 1 atmosphere of pressure for longer than six hours. Becker-Freyseng and Clamann¹³² made observations on 2 normal subjects who spent sixty-five hours in a gas-tight room containing 90 per cent oxygen. On the second day both felt uncomfortable, and in one there was a decrease in the vital capacity, associated with fever and a rapid pulse. On the third day one man felt especially ill and suffered from dyspnea, with a continuous fall in vital capacity. Behnke¹³¹ found that inhalation of 100 per cent oxygen to normal human subjects for seven hours produced substernal soreness and toxic effects. Moody and Howard¹³³ report a probable case of oxygen poisoning occurring in a two-year-old child acutely ill with lobar pneumonia. During one of her periods in the tent the patient developed convulsions, which subsided when

she was removed from the tent and returned shortly after she re-entered it. She was kept in the tent at frequent intervals for a period of six days. Unfortunately, no mention is made of exact oxygen-percentage determinations. It appears difficult to assify this case as one of oxygen poisoning.

Behnke¹³¹ stated that at atmospheric pressure ure oxygen is usually well tolerated by healthy persons over a period of six hours. An occasional healthy subject is particularly sensitive to it. The toxic signs and symptoms that may be observed at the higher atmospheric pressures are pallor, sweating, nausea, fatigue and irritability. These can be avoided by helium-oxygen breathing. Behnke and Arbrough¹³⁴ observed that at a depth of 500 feet, corresponding to a pressure of 16 atmospheres, a diver breathing a mixture of 80 per cent helium and 20 per cent oxygen felt nearly as well as at atmospheric pressure. In Behnke's experiments healthy subjects breathed pure oxygen at a pressure of 2 atmospheres for three hours without demonstrable harmful effects.

Although the cause of oxygen poisoning is unknown, Shaw, Behnke and Messer²⁹ demonstrated the remarkable relation between oxygen and carbon dioxide at increased atmospheric pressures. They showed in dogs at a constant pressure of 4 atmospheres that increasing the alveolar carbon dioxide tension was equivalent to raising the oxygen tension about 5 atmospheres. When the carbon dioxide tension was lowered by hyperventilation, the oxygen tension was decreased to about 3 atmospheres. At this high pressure the addition of carbon dioxide served to increase the toxicity of oxygen, whereas lowering the alveolar carbon dioxide tension by hyperventilation delayed or even prevented the onset of toxic oxygen symptoms.

Armstrong¹³⁵ further demonstrated the safety of high concentrations of oxygen in his studies on rabbits at decreased barometric pressures. With pure oxygen at a tension of 350 mm. of mercury — equivalent to an altitude of 20,000 feet — he failed to produce lung injury after an exposure of two hundred hours. This result has been repeatedly substantiated in aviators in more recent years.

Continuing their extensive studies on the effects of drugs on anoxia, Emerson and Van Lier¹³⁶ evolved a standard test to study the effects of drugs on the tolerance to anoxia in mice. They observed a slight increased tolerance to anoxia in mice pretreated with exposure to pure oxygen or to helium-and-oxygen mixtures. They did not, however, consider the mortality reduction in the control animals sufficient to conclude that the lethal effects of anoxia can be minimized with pretreatment inhalation of oxygen and helium-and-oxygen mixtures. They believed that their results could not be considered applicable to therapy in man without further investigation.

Clinical value. Under normal conditions increased concentration of oxygen has no effect on tissue function. Boothby and his associates^{4, 101, 102} demonstrated its value in the clinical anoxias. Inhalation of 70 to 100 per cent concentrations increases the partial pressure of oxygen in the lung, making it possible for the blood to absorb and transport a quantity in excess of the normal. The hemoglobin saturation can be raised from 96 to practically 100 per cent, and the oxygen in simple solution in the plasma from 0.3 cc. per 100 cc. of blood to a maximum of 2.2 cc. This represents a possible increase to as high as 15 per cent — supersaturation level — in the oxygen-carrying capacity of the blood throughout the circulatory system. This in turn produces a corresponding increase in the partial pressure available for the diffusion of oxygen from the blood into the tissues. In this connection, it will be recalled that Campbell and Poulton^{62, 137} demonstrated that the oxygen pressure in tissue is increased proportionately more than is the increase in oxygen content of the blood.

Evans¹³⁸ has for many years repeatedly described beneficial clinical results from so-called "100 per cent" oxygen in severe anoxia. Concentrations of 70 to 100 per cent should be used when lower concentrations are unsatisfactory. Boothby and his associates^{4, 13, 101} in extensive clinical observations proved the safety of high concentrations if used properly. They administered 90 to 100 per cent concentrations to approximately 800 patients for periods as long as forty-eight hours without any evidence of pulmonary irritation. They warned against continued administration for longer than forty-eight hours. Further clinical evidence showed that high concentrations can be used with safety with a mask apparatus for periods of two to five days. It is well to remember that mask therapy is really not continuous, inasmuch as the patient talks, eats or has the mask removed frequently for general nursing care.

In a recent paper Reinhard, Moore, Dubach and Wade¹³⁹ report on the effect of breathing 80 to 100 per cent oxygen in patients with sickle-cell anemia. They observed 3 patients at six different times, using the B.L.B. apparatus, with pure-oxygen flows without intermission for periods of eight to twenty days. They state: "No distinct toxic manifestations of the oxygen administration were noted except for inflammation and congestion of the mucous membranes of the upper respiratory passages. After oxygen was discontinued, 2 of the 3 patients became nauseated and had headache for twenty-four to forty-eight hours." My own clinical observations for periods of three to five days in patients with serious respiratory disease led to similar conclusions.

In closed respiratory chambers, such as the helium-and-oxygen hood apparatus, Barach¹⁴⁰ considers it inadvisable to use continuous oxygen

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30151

PRESENTATION OF CASE

First admission. A fifty-year-old man entered the hospital because of a draining abdominal sinus.

The patient had been in apparent good health until about ten months before entry, when he developed generalized abdominal discomfort, most marked in the lower midline. This was accompanied by tenesmus, but an attempt to move the bowels was unsuccessful. He became slightly distended, but had no nausea or vomiting. He was operated on the second day of the illness. The details of the examination and operative findings were unknown, except that a lower right paramedian incision was made and a drain was left in place. This drained feces for four weeks and continued to do so, although in a much reduced volume. Postoperatively he had normal bowel movements by rectum with the aid of 30 cc. of mineral oil daily. He had had no distention, pain, or bloody, tarry or mucous stools. His appetite had been poor. He had lost 20 pounds during hospitalization, but his weight had remained constant since.

He had had typhoid fever two years before admission, was hospitalized for several weeks, but recovered without any sequelae.

Physical examination revealed a well-developed, moderately well-nourished man, with evidence of recent weight loss. The heart and lungs were negative. The abdomen was soft and nontender. There was a small draining sinus in the midportion of an otherwise well-healed, low, right paramedian incision.

The blood pressure was 120 systolic, 80 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 4,920,000, with 14.9 gm. of hemoglobin. The white-cell count was 8800. The urine was negative. Stools were guaiac negative. A blood Hinton test was negative.

A barium enema passed without delay from the rectum to the cecum. The sigmoid was spastic, and

*On leave of absence.

several diverticula were visible in the distal sigmoid. The mucosa was swollen. Postevacuation films showed the sigmoid to be markedly irregular with a projection that was thought to be a fistulous tract. The remainder of the colon was contracted on the postevacuation film and displayed normal mucosal relief, except the ascending colon, which contained no barium. Re-examination of the colon showed marked irregularity of the wall of the sigmoid just above the rectosigmoid junction. There was no filling of the fistulous tract by enema. The cecum and ascending colon were spastic but filled symmetrically without filling defects. A lipiodol injection of the sinus tract showed ready passage of the dye to what appeared to be the sigmoid.

On the sixth hospital day a transverse colostomy was performed. Postoperatively the patient did well. The colostomy appeared to function well. On the third postoperative day he had a severe cramplike epigastric pain. Six hours later he vomited greenish, bitter material, and the vomiting persisted. The pain became intermittent. The abdomen was not distended, and peristalsis was normal. There were no masses or tenderness.

Plain films of the abdomen showed no dilated loops of bowel, but there was some gas scattered through the colon. At the level of the second lumbar interspace, there was a small round area of gas which was thought to be in the small intestine. Just above this a rounded area of increased density measuring 3.4 cm. was seen. This had a rather smooth margin.

A Miller-Abbott tube was passed. He had a good bowel movement through the colostomy opening with complete relief of symptoms. The Miller-Abbott tube was removed, and he was discharged home to return for another operation.

Second admission (twenty-four days later). Following discharge the patient had a bout of diarrhea lasting two or three days but was otherwise asymptomatic. His weight had remained essentially the same.

Physical examination was as before.

Examination of the blood showed a hemoglobin of 13.6 gm.

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. CARROLL C. MILLER: When the patient was admitted for the first time, he presented at first glance a perfectly definite and typical picture. If we were not for two complicating details, — namely, the gastrointestinal upset following the first operation and the visualization of a peculiar mass in the abdomen following this episode, either or both of which may or may not have anything to do with the final diagnosis, — it would be relatively easy to predict what was found at the second operation and the patient's subsequent course.

Let us, at the start, discuss the more likely underlying diagnosis. We see in the report and on the films that there was definite diverticulosis and probably diverticulitis of the sigmoid. When the patient first became ill, he complained of low abdominal pain, together with bowel tenesmus, difficult defecation and abdominal distention, but no nausea or vomiting. All these details are perfectly consistent with a diagnosis of diverticulitis in a middle-aged man. One aspect of the picture is slightly unusual. The onset was apparently abrupt, without prodromal signs of a disturbance in the lower bowel. People with diverticulitis frequently complain of difficulty in moving their bowels, tenesmus, and, occasionally, the passage of small amounts of stool over a period of some months or years. It is quite conceivable, however, that a bland type of diverticulosis may exist up until the time when a combination of physical circumstances arises to kick off a diverticulum, seal up an infection in it and initiate an inflammatory process that may lead to involve bowel wall and structures around the bowel. All that can occur in the course of a few days, presenting a picture that simulates a combination of low intestinal obstruction and peritonitis.

This is apparently what the first operator thought when he made his first incision. The possibility of acute appendicitis should not have been given much consideration because of the location of the most marked pain and the absence of nausea and vomiting. No mention is made of previous symptoms that could be attributed to a chronicolecystitis or cholelithiasis and that might contribute to the diagnosis we are attempting to establish.

We have, therefore, a man who, on first admission to this hospital, presented a story and completely satisfactory x-ray evidence of a subsided inflammatory reaction in the lower abdomen or pelvis, with establishment of a fecal fistula communicating with the sigmoid. In the x-ray films the presence of diverticula, the spasm and the irregularity of the lumen of the sigmoid substantiate such a diagnosis. The surgeon who performed the first operation in this hospital evidently felt the same way and subsequently performed a transverse colostomy in preparation for a subsequent exploration, with a view to ligating the fistula and removing the diseased bowel.

The intestinal complication occurring on the third postoperative day may have been due to an inflammatory reaction around the site of the transverse colostomy, causing a subacute intestinal obstruction. At that time the second complicating picture—namely, the flat abdominal

—this mass apparently was not visible in any of the previous films. It may have been obscured by some other denser structure and at that particular moment may have become obvious. I am

sure that I cannot guess what it was. One would like to postulate a gallstone that had eroded from the gall bladder into the small intestine and caused intestinal obstruction, but this mass was unusually large and it is unlikely that such a gallstone would cause no further trouble. A gallstone of such size would undoubtedly have great difficulty in passing the ileocecal valve and therefore would cause further obstruction, which the patient did not have. We are not told and cannot be sure where the mass lay in relation to the lumen of the bowel. It is conceivable that this was a scybalum of barium lasting over from the previous barium enema, but its density in the x-ray film does not appear to be that of residual barium. Consequently, although I am much perplexed by the appearance of this phenomenon, I cannot believe that it had anything directly to do with the patient's subsequent condition.

When the patient re-entered this hospital he was apparently in good condition and ready for the operation that had been planned. I am a little surprised that it was done so soon after the first, for I should suspect that insufficient time had elapsed to allow the inflamed sigmoid to become suitable for surgery. I should suppose that there was still induration with adhesions in the lower abdomen and pelvis, making exploration and resection difficult. My final diagnosis is diverticulitis of the sigmoid, with fecal fistula.

CLINICAL DIAGNOSIS

Diverticulitis of sigmoid, with sinus tract.

DR. MILLER'S DIAGNOSIS

Diverticulitis of sigmoid, with fecal fistula.

ANATOMICAL DIAGNOSES

Diverticulitis of sigmoid, with perforation.
Peritonitis, acute and chronic, localized, with matting of loops of small intestine.

Diverticulosis of sigmoid.

Meckel's diverticulum.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: At operation Dr. Arthur W. Allen found many coils of matted small intestine adherent to the anterior abdominal wall at a point midway between the symphysis and the umbilicus, just to the right of the midline. The sigmoid was completely collapsed and was drawn over into this mass of matted small bowel, which corresponded to the site of the fistula. When these loops were dissected free it was found that a Meckel's diverticulum, measuring 6 cm., was in the center of the mass. About 50 cm. of ileum, including the diverticulum, was resected, and a side-to-side anastomosis was performed. Then the sigmoid was resected with an end-to-end anastomosis.

When we received the specimen there were two small perforations of the ileum about 4 cm. from the

Meckel's diverticulum. These could have been made in dissecting away the adhesions or may have been produced by the localized peritonitis in the region of the fistula. The Meckel's diverticulum showed no evidence of intrinsic inflammation. The sigmoid, however, was markedly thickened and covered with a patch of fibrinous exudate, in the center of which was a small perforation 2 mm. in diameter that connected with a long diverticulum. This diverticulum was inflamed, and appeared to be the primary source of infection. In addition there were many noninflamed diverticula throughout the specimen.

Three weeks later the original colostomy opening was closed; the ends of the colon were resected, and an open end-to-end anastomosis was performed.

CASE 30152

PRESENTATION OF CASE

A seventy-nine-year-old retired factory manager entered the hospital because of persistent cough.

The patient had been in excellent health until six months before admission, when without antecedent upper respiratory infection he developed a paroxysmal cough productive of a small amount of thick, nonodorous, greenish sputum. This persisted until about six weeks before admission, when the amount of sputum increased to several tablespoonfuls daily. He developed a "smoky feeling" under the sternum at the level of the sixth rib, without definite pain. He had had no hemoptysis, chills, fever or weight loss. An x-ray film of the chest, taken two weeks before entry showed slight enlargement of the heart downward and to the left. The lower part of the right lung field was less radiant than normal. In the lateral view the outline of the middle lobe was easily seen, and its position corresponded to the area of fullness in the right lower chest. The interlobar septums were moderately thickened. The lung fields were otherwise clear.

The patient had been extremely active until six years before the onset of his present illness, when he was advised by his physician to "take it easy." Two or three years later he noticed shortness of breath on climbing two flights of stairs.

Physical examination showed a well-developed, well-nourished man. He was distressed by frequent cough. The trachea was in the midline. There was dullness posteriorly over the right clavicle. The breath sounds were increased and well transmitted. Many moist inspiratory and expiratory rales were heard over the right middle and upper lung fields. There was a loud moist wheeze over the whole right lower chest. The heart was slightly enlarged; the sounds were regular but faint. Examination was otherwise negative.

The blood pressure was 158 systolic, 88 diastolic. The temperature was 99.4°F., the pulse 85, and the respirations 24.

Examination of the blood showed a hemoglobin of 14.9 gm. The white-cell count was 6800, with 6 per cent neutrophils. The urine was normal. A blood Hinton test was negative. Another x-ray film of the chest, taken two weeks after the previous examination, revealed some increase in the size and density of the lesion on the right. There was no respiratory movement of the right half of the diaphragm. The outline of the diaphragm was irregular, and the right costophrenic sinus was shallow. The pleura was somewhat thickened along the axillary border.

On the third hospital day a bronchoscopy was performed.

DIFFERENTIAL DIAGNOSIS

DR. HELEN PITTMAN: May we see the x-ray films.

DR. MILFORD SCHULZ: The right middle lobe does not seem to me to be particularly decreased in size. I believe this represents its outline. There is hazy increased density overlying the right lower chest.

DR. PITTMAN: What about the pleural thickening?

DR. SCHULZ: There is a little on the right, and I wonder if the increase in density on the right side as compared with that on the left might not all be due to the thickened pleura.

DR. PITTMAN: What about the position of the diaphragm on the left?

DR. SCHULZ: It is elevated. A true paresis of the left half of the diaphragm, which would have been noticed fluoroscopically, was not observed.

DR. PITTMAN: There was true paresis on the right?

DR. SCHULZ: That must be accepted as the fluoroscopist's observation.

DR. PITTMAN: I do not believe that these films throw much light on the subject, and I am rather disappointed.

This seventy-nine-year-old man was in excellent health until the age of seventy-three, when he was advised to "take it easy." He had shortness of breath, which does not seem out of order for someone who is that old.

His illness began six months previously, when, without any prodromal symptoms and without any respiratory symptoms, he suddenly began to have paroxysmal cough and raised small amounts of sputum; this continued for a matter of four months or so. Then, for no apparent reason, the sputum increased in amount and became thick and yellowish and the patient developed a peculiar feeling, a "smoky" feeling, — whatever that means, — under the sternum at the level of the sixth rib. He did not have pain, did not spit blood and did not have chills, fever or weight loss. In other words, the only clue is that he had productive cough.

Physical examination showed dullness posteriorly on the right, over the right clavicle, which I suppose means the right apex posteriorly. "Breath sounds were increased and well transmitted." They usually are in that region of the chest. I do not believe that

that means so much. The loud moist wheeze over the right lower chest is the first thing that gives a localizing clue; the unilateral wheeze I interpret as a definite indication of partial obstruction of one bronchus on the right side — the middle or lower lobe, I do not know which. I should guess the middle lobe, but from the description and from these films I cannot be sure. He had slight fever, which seems noncontributory. He had no anemia and no leukocytosis, and the white count was normal, with a low normal percentage of neutrophils.

So we have here a man with a cough who had nothing to go with the cough and no evidence of infection beyond a temperature of 99.4°F. At no time had he had bleeding, pain, or anything that would lead one to suspect carcinoma, and of all the things that should make one suspect carcinoma, bleeding is the most significant. The absence of bleeding is important, but not necessarily diagnostic.

Then we come to the next positive finding, — the area of increased density in the right lower chest, — and I think that the only other definite positive finding is that there was no respiratory movement of the right half of the diaphragm. Why was there no respiratory movement of the diaphragm on the right? I do not know. We have nothing from the history, physical examination or x-ray findings to suggest that there was a process involving the phrenic nerve on that side. It is hard to think that he could have an aortic aneurysm involving the phrenic nerve with as little to go on as this.

The next point is, Did he have an acute pleurisy on the right side, which would cause immobility of the diaphragm? He had had no pain at any time, and the evidence of real pleurisy is extremely slim. I am sure that the immobility of the right leaf of the diaphragm is one of the most important findings, but there is not enough evidence to say with any certainty what caused it. So we are left with the area in the right lower chest. Whether these x-ray changes were secondary to the paralysis of the diaphragm, I do not know. I rather doubt it, because he was producing large amounts of sputum, and I am assuming that he had something in the bronchus causing partial obstruction, which was giving him this wheeze. We have no way of tying that up with the diaphragm unless we assume carcinoma, but there is no evidence on which one is justified in saying that this man had carcinoma.

How about a bronchial adenoma? I do not believe that we have enough evidence to postulate an adenoma, although that is one of the things that has to be seriously considered.

How about a nonopaque foreign body? It will cause a wheeze, but it is always associated with infection, and that is true everywhere else in the body. I do not see that we are justified in making that diagnosis.

Tuberculosis always has to be thought of, but again there is not much to go on. It is an unusual

site for tuberculosis, although that does not rule it out. In a seventy-nine-year-old man I should certainly expect more evidence of old tuberculosis elsewhere in the chest than we have in this x-ray film.

Is there enough evidence of old pleural infection to think he could have had at some time empyema and a bronchial fistula? There is absolutely no evidence for that, and again if it were active enough to have suddenly broken into a bronchus, with the patient evacuating empyema fluid out through his mouth, I should expect signs of infection and not an odorless sputum, although that is possible.

So I am left with a series of entirely unsatisfactory explanations for this man's condition. Because he had definite physical signs on the right side, and because he did have a wheeze heard only on the right side, I am going to cling to something in the bronchus, causing partial obstruction, as the most probable lesion. And because I have no evidence that satisfies me for carcinoma or for tuberculosis, I am going to call it adenoma, but with little faith.

DR. EDWARD B. BENEDICT: We did a bronchoscopy with a preliminary diagnosis of carcinoma, believing that in a patient of this age carcinoma was the most likely diagnosis. We did not pay enough attention to the fact that the patient had not lost any weight. Bronchoscopy showed widening and partial fixation of the carina, and a nodular outcropping in the right-stem bronchus causing partial obstruction of the right middle and lower lobes.

CLINICAL DIAGNOSIS

Carcinoma of the lung.

DR. PITTMAN'S DIAGNOSIS

Bronchial adenoma.

ANATOMICAL DIAGNOSIS

Tuberculosis of the bronchus.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: From the appearance that Dr. Benedict has just described it was thought that the diagnosis was probably carcinoma. The material that we received showed a granulomatous process, with one suggestive tubercle, although we did not have enough material to make a positive diagnosis of tuberculosis. It certainly looked suspicious of tuberculosis, however, and this was confirmed by examination of the sputum, which contained numerous tubercle bacilli. The patient therefore had tuberculous stenosis of the bronchus, probably with involvement of the mediastinal lymph nodes.

DR. BENEDICT: I have tried to keep in touch with this patient, and from hearsay, I have learned that he is doing well. He is going to an osteopath.

DR. CASTLEMAN: Are organisms still present in his sputum?

DR. BENEDICT: I do not believe that his sputum has recently been examined.

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PUBLIC OPINION AND COMPULSORY SICKNESS INSURANCE

THE Wagner-Murray-Dingell Bill has provoked a great deal of discussion among physicians. Numerous editorials and articles have appeared in medical journals, and it is fair to assume that most doctors have thought somewhat about the significance of Title IX of the bill and know how most of their colleagues react to it. On the other hand, what other professional men and laymen think about the medical aspects of the bill is less clear. It is known that soon after the bill was introduced into Congress, the leaders of both national labor organizations issued statements strongly supporting it.

Furthermore, editorials have appeared in the press both for and against this proposed legislation.

Some time ago the American Bar Association appointed a committee to study the medical provisions of the bill, and its report, which was reprinted in the March 11 issue of the *Journal of the American Medical Association*, is well worth reading. The preamble to its conclusion is as follows:

The American Bar Association is limited to an expression of opinion and judgment with respect to those fields which relate to the administration of justice and which directly affect the safeguards and protection of the rights and liberties of the citizens of this country. Under normal circumstances, therefore, it is not the function of this association to attempt to influence substantive legislation by the Congress of the United States. But when, under the pretext of the general welfare, legislation is proposed in Congress which either inadvertently or with deliberate subtlety constitutes a direct attack on the rights and liberties of the citizens of this country, it becomes the duty of this association actively to voice its objections. . . .

It is apparent that the main objections of the committee are based on the powers vested in the Surgeon General of the United States Public Health Service, without machinery of appeal, and the vicious system of federal control, without safeguarding the rights of patients, hospitals and physicians.

Another important point of view is furnished by a comprehensive survey recently made for the National Physicians Committee and published in a booklet entitled *The American People*. This should be read and studied by every physician and should be passed along to his patients and friends. It is quite evident from this survey that the majority (84 per cent) of the people, including industrial workers, are unwilling to pay the cost of a federal health system, and that 68 per cent will have nothing to do with it regardless of cost. A significant fact to be gleaned from the survey, however, is that 63 per cent of the people *do* want some form of prepayment sickness insurance. This warning cannot be ignored.

The extraordinary success of the Blue Cross, both in Massachusetts and elsewhere, can leave no doubt in anyone's mind that voluntary organizations are able to provide adequate hospital care if they are well administered. Furthermore, it seems likely that voluntary insurance schemes for covering the costs of medical care will prove to be equally effective. Many such plans are already in operation, including

the Blue Shield, sponsored by the Massachusetts Medical Society, but at the moment they do not cover the needs of enough people. It is evident that the laity do not want compulsory health insurance sponsored by the Government. 85 per cent of the people believe that their physicians have a personal interest in them and that this would be lost under federal control. Nonmedical people are looking to the medical profession for leadership in providing complete prepayment sickness insurance on a voluntary basis.

acute entzündliche Knochenatrophie [Concerning Acute Inflammatory Atrophy of Bone], published in the *Archiv für klinische Chirurgie* (62:147-156, 1900). A portion of the translation follows:

The bone atrophy that occurs in association with acute inflammatory affections of the bones and joints occupies a special place in my opinion and is essentially different from the simple atrophy of disuse. In the latter, for example, atrophy occurs to any considerable extent only if the functional stimulus has been lacking over a long period of time — at least a few months, — whereas in what I have referred to as acute inflammatory affections of the bones and joints a significant degree of atrophy takes place in a remarkably short period of time, not only indeed in the bones directly involved, but also in the neighboring bony structures that are functionally related to the diseased bone.

R W B

FORT DEVENS CONFERENCE ON MILITARY SURGERY

THE Conference on Military Surgery presented by the surgical staff of the Lovell General Hospital at Fort Devens on March 30 was attended by 46 medical officers of the United States Navy as well as by 127 civilian physicians from various parts of New England, the total attendance being 284. The conference was an outstanding success and clearly demonstrated the high grade of clinical and laboratory procedures used by the armed forces. The subjects of penicillin therapy and reconstruction of intestinal wounds and a motion picture study of the rehabilitation of the wounded soldier were of especial interest.

Such conferences are the complement of the monthly graduate courses presented by civilian instructors under the auspices of the New England Committee for Wartime Graduate Medical Meetings at twenty different stations of the Army and Navy throughout New England, beginning last November.

It is of further interest to know that both the Army and Navy plan to have exhibits at the annual meeting of the Massachusetts Medical Society in May. Details about these exhibits will be published in the final program.

MASSACHUSETTS MEDICAL SOCIETY COMMITTEE ON LEGISLATION

Public hearings will be held in various cities of the Commonwealth to study the possibility and desirability of a system of cash payments to persons who become unemployed because of illness or accident not otherwise covered under the Workmen's Compensation Act.

The Massachusetts Legislature, by Chapter 54 of the Resolves of 1943, placed the responsibility of the study of such a program with the State Advisory Council of the Massachusetts Division of Employment Security. Public hearings, conducted by this body, are scheduled as follows:

Lawrence	April 17	Council Chambers, City Hall 2 30 p.m. and 7 30 p.m.
Fall River	April 20	Council Chambers, City Hall 2 30 p.m.
New Bedford	April 20	Room 20, City Hall 7 30 p.m.
Springfield	April 26	Room 212, City Hall 2 30 p.m. and 7 30 p.m.
Pittsfield	April 27	Council Chambers, City Hall 2 30 p.m. and 7 30 p.m.
Worcester	April 28	Council Chambers, City Hall 2 30 p.m. and 7 30 p.m.
Boston	May 1	10rd Hall, 15 Ashburton Place 2 30 p.m. and 7 30 p.m.

The Advisory Council, through these hearings, is seeking to obtain the reactions of the people of Massachusetts to the need of such a program. The following questions are pertinent: (1) Is there the need of a compulsory program of cash benefits for sickness or nonindustrial accidents in the Commonwealth of Massachusetts? (2) If such a program should be adopted, should it become a part of the present unemployment compensation program or is it in fact an inseparable part of a general health program which, if adopted, should be administered by some other department, such as the Department of Public Health? Is the country ready for a general health program? (3) If desirable to adopt a state system of sickness benefits, how should it be financed? Can the Massachusetts worker afford to pay for any further expansion of the social security program?

MEDICAL EPONYM

SUDECK'S ATROPHY

Dr Paul Sudeck (b. 1866), professor of surgery at Hamburg, was the author of a paper, "Ueber die

Should the system be financed by employee or worker contributions only? By employer contributions only? By a combination of both? Or by a combination of employer, employee and state contributions? (4) Is such a program of a social or public interest? If social, should not all the residents of the Commonwealth be included in the program instead of confining the same to workers covered under the present unemployment compensation program?

The above is an outline of the type of questions involved and to which the Advisory Council wishes to obtain an expression of opinion on the part of the general public prior to making its report to the General Court. The members of the State Advisory Council of the Massachusetts Division of Employment Security are Morris B. Lambie, chairman, Henry Cloutier, Joseph Cabral, Mary M. Riley, Fred W. Steele and Alfred E. Rankin.

All parties interested in this matter are cordially invited to attend.

BRAINARD F. CONLEY, *Chairman*

DEATHS

COLBURN — Frederick W. Colburn, M.D., of Boston, died April 9. He was in his seventy-fourth year.

Dr. Colburn received his degree from the Boston University School of Medicine in 1897. In 1899 and 1900 he did postgraduate work at Vienna, Austria, and Halle, Germany. Shortly after his return to Boston, he became assistant instructor of otology at the Boston University School of Medicine. At the time of his death he was professor emeritus. He joined the staff of the Massachusetts Memorial Hospitals as assistant aural surgeon and later advanced to surgeon-in-chief of the Ear, Nose and Throat Department. He was a member of the Massachusetts Medical Society, the American Medical Association and the American Homeopathic Ophthalmological, Otological and Laryngological Society and a fellow of the American College of Surgeons.

A daughter, two sons and a brother survive.

GLEASON — Edward F. Gleason, M.D., of Boston, died April 9. He was in his seventy-sixth year.

Dr. Gleason received his degree from the University of Vermont College of Medicine in 1899. He studied surgery at the University of Vienna and on his return established practice in Boston. He was one of the first members of the staff at Cape Cod Hospital, Hyannis, which was founded in 1920. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, two daughters and two sisters survive.

LEMAIRE — Willard W. Lemaire, M.D., of Worcester, died January 27. He was in his sixty-sixth year.

Dr. Lemaire received his degree from the University of Vermont College of Medicine in 1902. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, a son and a daughter survive.

MERRICK — Francis H. Merrick, M.D., of Boston, died January 17. He was in his thirty-eighth year.

Dr. Merrick received his degree from Boston University School of Medicine in 1933. He served on the staffs of the Boston City and St. Elizabeth's hospitals. He was a member of the Massachusetts Medical Society and the American Medical Association.

PARKS — Silas H. Parks, M.D., of Great Barrington, died November 7. He was in his eighty-third year.

Dr. Parks received his degree from the Albany Medical College in 1885. He was a member of the Massachusetts Medical Society and the American Medical Association.

MISCELLANY

TUBERCULIN TEST, X-RAY AND OTHER DIAGNOSTIC AIDS

To diagnose the greatest possible percentage of unsuspected cases of tuberculosis, to place these people under immediate and adequate care, to render them and the community safe from further spread of their disease, to rehabilitate every patient into a productive member of society — these are our tasks. Diagnostic procedures that guarantee the maximum return in case finding are those that safely apply the clinical lessons of the past to the pressing problems of the present. No thorough clinician relies exclusively on a solitary diagnostic aid, even when circumstances strongly tempt him to do so. These points are clearly brought out in the following paper (Myers, J. A. Tuberculin test, x-ray and other diagnostic aids. *Journal-Lancet* April, 1944).

There is now a strong tendency to "diagnose" tuberculosis by short-cut and sometimes slipshod methods. Recently, a few physicians were asked how they would proceed to find all the tuberculosis among the population of an entire industry or county. One stated that increased red-cell sedimentation rate would ferret out all cases. Another would discover them by finding acid-fast bacilli in their sputums. Still another would employ only x-ray-film inspection of their chests. Other similar methods were offered. Each physician presented an important phase of an examination, but not one of them was adequate. To achieve a satisfactory diagnosis each one of this group of physicians would have to examine a given individual in his own way, then pool his findings with those of his colleagues — a wasteful and illogical procedure.

There can be no tuberculosis in the absence of tubercle bacilli; therefore, the first phase of an examination is to determine whether bacilli are present. This can be done by the tuberculin test, which is accurate and specific except in the first few weeks after infection occurs, and in acutely ill and terminal cases. Other failures are usually due to the use of impotent tuberculin or to improper administration. Under proper conditions, then, a nonreactor to tuberculin can be told that he does not have living tubercle bacilli in his body. On the other hand, a reactor has at least primary lesions that contain living tubercle bacilli. Exceptionally, and only when all bacilli die, allergy persists for a time, then wanes and disappears. Inasmuch as primary tuberculosis is a prerequisite for the clinical forms, it is of extreme importance to know whether it is present. The tuberculin test provides this information with uncanny accuracy. With the exceptions mentioned, it is with great rarity that the person with clinical tuberculosis fails to react to tuberculin.

The next phase of the examination consists of inspecting the chests of all adult reactors with the x-ray. On the ordinary film 25 per cent of the lung parenchyma is obstructed from view by shadows of such parts as the heart and diaphragm. Films fail to reveal evidence of primary tuberculosis in 70 to 80 per cent of the persons in whom it actually is present. So, too, many lesions of the reinfection type, because of their size and consistence, escape detection. It is a frequent experience to view a film that appears clear, yet one of the same chest a few months later reveals evidence of disease. Therefore, adult tuberculin reactors whose lungs appear normal should have films at least annually.

After tuberculous lesions of the reinfection type attain macroscopic proportions, x-ray inspection is by far the best method of detecting their locations when they are in that part of the lung which is visualized; indeed, they cast shadows on an average of two or three years before they cause significant symptoms. Final diagnoses, however, should never be made from x-ray shadows, since those cast by tuberculous lesions may be indistinguishable from those of numerous other pulmonary diseases, such as sarcoidosis, silicosis, malignant tumor, fungus infections, abscess and pneumonia. When a lesion is found, its etiology can usually be determined by other methods.

The present, widely used procedure that begins with x-ray inspection of the chests of large groups of adults is laudable, provided it does not end there. All concerned must be informed that x-ray inspection is done with the unaided eyes and reveals nothing but macroscopic lesions, that one fourth of the lung parenchyma is obstructed from view by shadows of other parts and that final diagnoses cannot be made with accuracy from x-ray shadows. Thus, the tuberculin test screens out those persons who have living tubercle bacilli in their bodies, and from them the x-ray screens out those who have gross lesions that may be tuberculous. Neither nor both procedures constitute an adequate examination.

To determine whether a demonstrable lesion is tuberculous one must seek tubercle bacilli in material obtained from it. Among patients with extensive tuberculous lesions these are usually promptly recovered from the sputum. When bacilli are not found in more than one of several specimens, or if no sputum is present, gastric lavage may reveal their presence. Visualizing acid-fast organisms by the aid of the microscope may not be sufficient because of laboratory errors and also because nonpathogenic, acid-fast bacilli are sometimes found in the sputum and gastric contents; therefore, their pathogenicity should be determined by culture on an artificial medium or by animal inoculation. In the event tubercle bacilli or other pathogenic organisms are not recovered, one should observe frequently new x-ray films to determine whether abnormal shadows persist or any significant changes occur in or around them. Among persons beyond thirty-five years, however, one should avoid delay, as the lesion may be malignant. In such cases the bronchoscopist should be consulted, as he may promptly reveal the etiology.

There is no more deplorable practice than to have tuberculin tests administered and x-ray films prepared, after which the physician makes diagnoses without seeing the subject and completing the examination. The subject should always be interviewed by the physician. Although most persons have no symptoms for an average of two or three years after the disease can be located, and practically none of those with primary tuberculosis give histories of significant illness, the tuberculin reactors whose chest films are entirely clear may relate symptoms caused by extrathoracic tuberculosis. In fact, acute conditions, such as meningitis and miliary disease, or chronic lesions in such parts as the kidneys, pelvic organs, and bones and joints may be developing.

Following the interview, even though no significant evidence is obtained, the remainder of the traditional physical examination should be made, since significant pulmonary signs may be elicited from lesions located near the periphery or in parts of the lungs not visualized by x-ray, moreover, lesions may be found during the scrutiny of extrathoracic regions.

To summarize: Tuberculosis begins when the tubercle bacilli first enter the human body and are focalized in microscopic lesions. At that stage the disease may lie dormant or may even disappear. Again, it may undergo exacerbations and remissions resulting in every form of clinical tuberculosis to which the human body is heir. The physician can diagnose tuberculosis within a few weeks after the first invasion of tubercle bacilli, and he can detect most of the subsequent lesions with considerable promptness. Either to diagnose tuberculosis when it does not exist or to fail to find it when it is present, is inexcusable. Nearly all errors in diagnosis are due to short-cut or slipshod methods and may be avoided by employing every phase of a complete examination — Reprinted from *Tuberculosis Abstracts* (April, 1944)

THE WHITE PAPER ON THE NATIONAL HEALTH SERVICE

The following statement was recently released by the Information Division, British Information Services, 30 Rockefeller Plaza, New York City.

* * *

The White Paper on National Health Service published by the Ministry of Health and the Department of State for Scotland on February 17, 1944, is the latest in a series of far-reaching plans for the social development of Great Britain. It sets out to fill the gaps in Britain's already extensive medical services and "to make a complete range of medical services of the highest quality available to all."

The White Paper represents the considered opinion of the Government, but not its final decision. The proposals will be freely examined and discussed in Parliament and throughout the country. Discussions will be

held with representatives of the medical profession, local authorities, voluntary hospitals, pharmacists and so forth. In the light of the constructive criticisms thus obtained, legislation will be proposed later in the year. Copies of the White Paper are being sent to 50,000 doctors practicing in Great Britain, or serving in the armed forces, and their comments on the scheme are invited.

This Paper is not to be confused with the White Paper on social insurance (arising out of the Beveridge Report), which is still in preparation. It does, however, aim at the fulfilment of Assumption B of the Beveridge Report — the assumption of comprehensive health and rehabilitation services for all as a basis for comprehensive social insurance.

Medical Facilities

Complete free medical facilities — general and specialist, are to be easily available to all. These will include the following:

General medical care. General medical care will be supplied by a general practitioner for every man, woman and child. Free choice for both patient and doctor is to be preserved. As under the present National Health Insurance scheme, patients will be free to employ a general practitioner, if they wish, and doctors will be free to have a private as well as a public practice. It will be possible to choose their own doctor, who would visit them in their homes if necessary. The more expensive medical services will be worked out by pharmaceuticals and co-ordinated hospitals to the hospital where the essential part of national health care will be provided. Patients will be invited to take part in the national scheme under their own management, but under compulsion to observe the general conditions. In return they will receive certain service payments in accord with centrally determined scales, but less in amount than the actual cost of the services rendered. (If the voluntary hospitals are to be maintained they must continue to rely largely on their own resources and private benefaction.) Certain other payments will also be made to the hospitals from the Central Fund in respect of their help in the scheme, and it is suggested that the hospitals may wish to make one fund of these, from which allotments could be made to individual hospitals according to their need.

There will be no interference with the internal management of voluntary hospitals — no surrender of their independence or change in their status. All hospitals will be visited and inspected by experts who will keep the largest advance in medical science. These will be available through health centers or in the home. They will call in consultants and staff of the hospitals. Special of consultants and to spread remuneration and conditions as well as to spread on the hospitals, although group practices and health centers will also offer more specialized treatment than the average general practitioner can offer today.

Maternity and child welfare services. All the present institutional arrangements, in hospitals and maternity homes, for maternity cases will be maintained.

Domestic medicine and nursing. The new Education Bill and the present White Paper envisage that the education authorities will retain the function of inspecting school children and encouraging necessary medical treatment. When the new health service is inaugurated, however, children as well as adults will look to it for medical treatment.

Tuberculosis dispensaries, cancer diagnostic centers and mental clinics. All these will be outpatient activities of the reformed hospital and community service.

Service of this type will be taken to increase the supply in, young people and expectant mothers.

It will be to ensure that those ill be able to obtain it with out charge. The scheme will probably be administered by county and county-borough councils.

Organization and Remuneration of General Practitioners.

There will be no compulsion on doctors to join the National Health Service, but it is expected that the great majority will do so, as the great majority have joined in the present National Health Insurance scheme. Doctors who take on a public practice will be free to have a private practice also. The numbers of private patients will inevitably be reduced, however, as equally good treatment and care will be available free in the public service.

In order to ensure equality of conditions of public service throughout the country, it is proposed that the general practitioner service will, in the main, be centrally organized.

The Central Medical Board, appointed by the Minister of Health, will be responsible for much of the administration of the service and will act as "employer" of doctors who take part in the service. It is with the board that doctors will enter into contract. (Doctors in health cen-

ters will enter into a three-sided contract with the Central Medical Board and the local authority.)

As described above, doctors will be free to join the public service either in separate practices, in group-practices or in health centers. It is proposed that young doctors fresh to the service should start their work as apprentices to more experienced general practitioners.

The proposals of the White Paper as regards remuneration of doctors do not envisage a system under which all doctors engaged on public service would be paid by salary. It is suggested instead that, whereas doctors in health centers should be salaried workers in order to prevent any competition for patients, those in separate practices should normally be paid according to the number of public patients in their care — a capitation system similar to that now used under the National Health Insurance scheme. Doctors in grouped practices other than health centers will be able to choose which method they prefer. It is proposed that the maximum number of patients that any one doctor may care for should be regulated. A doctor having a private as well as a public practice will be allowed fewer public patients, and thus less public remuneration.

Although there will be no interference with doctors who wish to go on practicing where they are and to take part in the local public service, there will be regulation of the entry of doctors into new practices, in order to ensure reasonable distribution throughout the country. Doctors wishing to set up a new, or take over an existing, public practice will have to obtain the consent of the Central Medical Board. If the area is "over-doctored," permission may be refused. The Joint Authority will be responsible for the integration of general medical practice within the general area plan — including arrangements for the numbers and distribution of doctors and their liaison with hospital, specialist, clinic and other services in the area.

The sale of practices will clearly be affected by the regulation of doctors entering new practices. A doctor giving up his practice in an "over-doctored" area may find that the board will not permit his practice to be purchased. Again, practices within a health center will not be saleable. Thus a doctor who leaves a private practice for a health center will be exchanging a practice that he can sell for a practice that he will be debarred from selling.

To remedy these cases of hardship a scheme of compensation for practices that lose their value and a superannuation system for doctors in health centers will be organized. The whole question of the sale and purchase of public practices is to be discussed with the profession, particularly with a view to preventing the new public service from increasing the value of any individual practice.

Administration

Central responsibility to Parliament and the people will rest with the Minister of Health. Advising the Minister, but independent of him, there will be the Central Health Services Council, which will provide professional guidance on the technical aspects of health service. This would represent the main medical organizations, the hospitals, medical teaching, dentistry, pharmacy, nursing, midwifery and so forth.

In accordance with principles of decentralization and with present practice, county councils and county boroughs will be responsible for securing comprehensive and general health services within their areas.

But in order that the most efficient specialised services may be available for all areas, it will be necessary for certain areas to co-operate with each other.

Areas able to provide complete and self-contained hospital and specialist organisation will be designated by the Minister of Health after consultation with local bodies. County councils and county-borough councils in these areas will form joint authorities to administer hospital, consultant and allied services. Each joint authority will have the responsibility of planning the whole of the area's medical services, although actual provision and management of certain local services will be the responsibility of the individual county councils that form the Joint Authority. Alongside each new authority there will be a local health-services council — a professional and expert consultative body.

Local operation of child-welfare services will be the responsibility of the local authorities.

There will also be the Central Medical Board which, unlike the Central Health Services Council, will have executive functions in the working of the general practitioner service.

The Service in Scotland

The scope and purpose of the National Health Service will be the same in Scotland as in England and Wales. The above proposals will apply generally to both countries, subject to a few administrative differences.

Central responsibility will rest with the Secretary of State for Scotland. There will be a separate Central Health Services Council and a separate Central Medical Board for Scotland.

As local government organization and geographical features are different, the local administrative structure cannot be identical. About 80 per cent of the population of Scotland is concentrated in 17 per cent of the total area. Over wide areas there is a very sparse population, and local government units there lack the resources of urbanized England and Wales.

The five natural hospital regions of the country — based on Glasgow, Edinburgh, Aberdeen, Dundee and Inverness — are too large to serve as administrative units. It is proposed that each of these areas should have a regional hospitals advisory council with consultative and advisory functions. The actual administration of the hospital and consultant services would be entrusted to joint hospital boards, to be set up for smaller areas within the regions. (Thus the advisory and executive functions of the joint authorities in England and Wales would be divided in Scotland between two bodies.)

Clinics and other services not closely allied to the hospital service will remain in the hands of the major health authorities, who will be required to combine where necessary for the efficiency of the health service.

Health centers will be directly provided and administered by the Secretary of State for Scotland instead of by the local authorities, as in England. Instead of local health services councils there will be a local medical services committee for every joint board area. This will advise on the development of the general practitioner service and act as liaison between this and other parts of the National Health Service.

Finance

It is estimated that the total annual cost of the National Health Services will be about \$592,000,000, compared with about \$244,000,000 spent from public funds on the present health services.

The cost will be met both from central and local public funds. The extent to which these will be made up by contributions under a social insurance scheme remains to be considered in the forthcoming White Paper on social insurance.

The State itself will spend directly about \$134,000,000 on the new general practitioner service, including payments to chemists and the whole cost of health centers in Scotland. It will also give a grant of 50 per cent to help county and county-borough authorities to meet the increase in the total cost of the health services. The grant will be adjusted to give more help to poor areas and less to rich. Every new service other than the hospital and consultant service (health centers, dental and ophthalmic services and home nursing) will be assisted by 50 per cent grants. Joint authorities will receive a grant of \$400 a bed (\$140 in mental and infectious disease hospitals) in aid of hospital and consultant services. A similar grant will be paid to voluntary hospitals.

Conclusion

In conclusion it should be observed that the National Health Service will not only aim at the abolition of ill-health but at the positive improvement of good health. Its fundamental object is best expressed in the introduction to the White Paper, where it is stated that the Government wishes to ensure for every man, woman and child "that what they get shall be the best medical and other facilities available; that their getting these shall not depend on whether they can pay for them or on any other factor irrelevant to the real need — the real need being to bring the country's full resources to bear on reducing ill-health and promoting good health in all its citizens."

NOTE

The appointment of Dr. Alfred L. Johnson, professor of clinical dentistry, as administrative officer of the Harvard School of Dental Medicine and associate dean of Harvard Medical School, has recently been announced. The School of Dental Medicine on March 31 assumed responsibility for all dental education and research at Harvard University, succeeding the Harvard Dental School, the oldest university dental school in the United States, having been founded in 1867.

CORRESPONDENCE

A VISIT TO A TUBERCULOSIS SANATORIUM IN NORTHERN ICELAND

To the Editor: Five miles south of Akureyri, on the sharply rising land on the west side of the Eyjafjörður (Island Fiord), one can see the white walls of a three-story building of rather imposing size and pleasing appearance. A drive of easy grade from the main road soon brings one to the entrance of the large central building. The latter nestles against the hillside surrounded by smaller outlying structures, presenting the same white walls and clean-cut modern lines. This was the Kristnes Tuberculosis Sanatorium, which I had been eager to visit ever since I had first viewed it shortly after my arrival in the northern part of Iceland. No doctors I had known had visited it, so I was convinced that if I was to learn a little of how the Icelandic Government takes care of its citizens with tuberculosis, I should do well to visit one of their sanatoriums, of which Iceland has two. I had read that tuberculosis in Iceland has been for many years one of the chief causes of death among the adult population. Besides, I had heard many extravagant rumors about the disease, such as the one asserting that almost everybody on the island is supposed to have had it (at one time or another) and that one can catch it very easily. For more reasons than one I was eager to find out some facts for myself.

A week before my visit I had been instructed by an Icelandic friend of mine just how to ask for the physician in charge. Diligently I memorized the phrase, which phonetically sounded much like this: "Git yerkt tal lath with Rafnar Laeknir?" Translated it meant, "May I speak with Dr. Rafnar?"

With these few words on the tip of my tongue, I set out one afternoon for the sanatorium. In a short time I arrived at the small courtyard in front of the main building. From almost every window facing in my direction many people stared at me; these were the patients, and apparently the sight of a uniform was unusual for them. Considering their prolonged confinement, I realized later that their curiosity was only natural. A simple doorway led into a long corridor where patients were lounging; there was no vestibule or lobby. A young man stood just inside the door, apparently directing other visitors to the various parts of the hospital. In the phrase I had remembered, I asked him if I might speak to Rafnar Laeknir.* The wording and accent must have been fairly correct, as he quickly nodded and turned to

*It is the custom in Iceland for most physicians to be addressed by their first name followed by Laeknir — hence, Rafnar Laeknir.

guide me to a large two-story concrete house across the courtyard. Rafnar's apartment occupied the second floor. I knocked on his door and even called out his name, but all was silent and it was evident that the doctor was not at home.

Returning to the hospital, I found the man who had given me my first directions. He soon located the other resident physician, Richard Laeknr, who cordially greeted me. Fortunately he could speak English well enough for us to understand each other. He said he had plenty of time to talk and to show me whatever he could, so I felt reassured that I would after all learn something about the sanatorium in spite of the fact that I had not been able to locate Rafnar. It was not long before we were engaged in a lively conversation.

His office led off the long corridor, which I could now see was on the second floor. There were two rooms in the outer one were a doctor's office and a waiting room.

containing for with German was a fairly

Richard Laeknr did much of the roentgenographic work of the hospital. His basic medical training had been obtained at the university in Reykjavik, which he attended for five and a half years. He then went to Denmark for instructions in obstetrics, as no course on that subject was given in Iceland. Shortly after this, his final examinations were finished and he received his doctor's degree. A year of internship followed in a Danish hospital, during which time he contracted pulmonary tuberculosis. Soon, however he was back at work as resident at a tuberculosis sanatorium near Jutland. After two years there he returned to Iceland. About six years ago he accepted his present position as the junior resident physician in this sanatorium.

At this point Richard Laeknr asked me if I cared to be shown about the hospital, and I was quick to assent. We first made the rounds of the rooms, which faced south as did the kitchen, dining room and the two large porches. The patients' beds were rarely more than two or three feet apart, no cubicles or screens between the beds were visible. The hospital was overcrowded, having twenty more patients than normally, the census was eighty. This overcrowding I later learned, was not limited to Kristnesi, at Vífilsstaðir, the first tuberculosis sanatorium to be established in Iceland (1911), there were one hundred and eighty patients in a building planned for ninety. As Richard Laeknr and I were making our visit all the patients were resting quietly in bed for it was the early afternoon rest period. Richard Laeknr then told me that the buildings at Kristnesi had been erected in 1927.

We next stepped out on the two large porches, one reserved for men, the other for women. These were unoccupied at the time, but many steel beds were stacked up against the back walls, on the north side of the verandas. When the weather is pleasant and it is not too cold or windy, certain selected patients are permitted to use the beds. The latter are provided with mattresses and either sacks lined with sheepskin with the wool turned in, eiderdown comforters or woolen blankets (an important Icelandic product). This form of therapy is given more for the value of fresh air than for the exposure to direct sunlight, since most of the cases are of the pulmonary type.

Back in the main building on the first floor we passed through a spacious kitchen that appeared to be clean and well aired. Large windows on the south side admitted light to every part of the room. On the floor just above was a dining room in which a partition was being torn down. The sanatorium had just bought an excellent cinema projector equipped for sound, and more space was desired for the showing of American and British films. We next stopped in at one of the pantries, the eating utensils had been put away in a clean, orderly fashion, but Richard Laeknr demonstrated the large steam sterilizers in which they were placed, after being carefully washed. On the third floor we visited a small clinical laboratory where simple tests were carried out. Specimens of sputum (*kraki*) were examined on glass slides, using the Ziehl-Neelsen technic.

Returning to his office, we made ourselves comfortable in two of the straight backed chairs and continued our talk. I asked him if he would kindly give me more details regarding the treatment of his patients, he said he still had plenty of time to spend with me and would be only too glad to tell me all he could.

Patients are admitted to the two tuberculosis sanatoriums in two ways, one, directly from the patient's own physician, the other, through one of several state supervised tuberculosis stations, which are scattered throughout the island. On the patient's discharge from either of the sanatoriums, a brief summary of the clinical record is forwarded to the tuberculosis officer in Reykjavik, who is responsible for its incorporation in the public health records.

At Kristnesi any patient who has a fever must stay in bed at all times. No reclining chairs are used but patients may be propped up in bed with pillows if this makes them feel more comfortable. For those who are afebrile and whose disease is evidently nonprogressive, a graduated scale of exercise is arranged. At first, they are allowed up between noon and 1 p.m. for several days, if they continue to remain afebrile and symptomless the hours of being up are gradually increased over a period of weeks until the patients are up the whole day — 8 a.m. to 9 p.m. — with the exception of the rest periods during which they are supposed to sleep.

A patient's schedule for the day ran fairly close to this:

7 00 a.m.	At se
8 00 a.m.	Breakfast (Morgunnatur)
10 10 a.m. to 11 30 a.m.	Rest period
12 00 noon	Dinner (Hádegismatur)
2 00 p.m. to 3 30 p.m.	Rest period
3 30 p.m.	Coffee cocoa or milk with cakes and bread
5 30 p.m. to 6 30 p.m.	Rest period
7 00 p.m.	Supper (Aðdegismatur)
9 15 p.m.	Light out
8 00 p.m. to 10 00 p.m.	Cinema (usually held once a week)

The patient who continues to improve under this program may in time take short walks once to three times a day for periods of fifteen minutes increasing to one hour, if he tolerates outdoor weather. Pneumothorax treatments are given by either of the two resident physicians. This form of therapy is attempted in all the pulmonary cases and when it fails to produce the desired result, more complicated procedures are resorted to (pneumolyses, phrenicorrhexes, rib resections and so forth). About six operations of this type are performed each year at the Akureyrri Hospital (*Sjúkrahús Akureyrar*) by its chief surgeon Gutmundur Karl Laeknr (Pétursson), who at the time of my visit was attending a meeting of the American College of Surgeons in Philadelphia. Patients who for one reason or another are not able to receive this care are required to adopt longer rest periods and a more graduated treatment schedule.

Patients with evident tuberculous involvement of the pleura without demonstrable pulmonary infiltration of the lymph nodes or of the skin are encouraged to expose themselves to the direct rays of the sun or to sun lamps. Kristnesi has one of the mercury vapor type. Exposure is carefully regulated. Treatments at first are brief, later the exposure periods are increased to suit the toleration of the patient.

At night and during rest periods, the windows of the patients' rooms, which are large even by our standards, are kept open as widely as possible. Frequently however, they have to be kept closed owing to the high winds so common in this region. Draughts are sedulously avoided to minimize air-borne spread of the tubercle bacilli. The main building had ventilating conduits but as a result of a roof fire the previous year, these had had to be blocked up. It is realized that the present ventilating system is unsatisfactory, but funds for its improvement are lacking.

The patients are encouraged to keep their minds occupied with varied interests. Although no formal occupational therapy work is done at the sanatorium, ambulatory patients do a considerable amount of weaving on small light wooden frames that can be held in the lap, knitting and embroidery are popular with the women. The value of this type of therapy is being increasingly appreciated in the sanatoriums in Iceland, and plans have already been arranged at Kristnesi for the construction of a separate building for looms, drawing boards, woodworking benches and so forth. Richard Laeknr thinks that poor patients can do with their hands or feet is helpful for nonpsychotic depressive moods, in addition, he believes that the patient may develop more resistance while thus occupied that this work makes the time pass more quickly and finally that it is well to have those who are going home to more or less heavy household and farm work prepared to use their bodies, particularly their hands and feet.

The hospital stay varies from two months to ten years. Since almost all the patients are unable to pay the full cost

of their treatment, their expenses are partially or wholly defrayed by the State. Approximately 70 per cent of the patients admitted to Kristnesi or the other tuberculosis sanatorium are discharged healed or practically so. Richard *Laeknir* did not have figures available to show what the exact results were.

The sanatorium provides training for two student nurses at one time; each spends six months there as part of her nursing course, most of which is taken at the University Hospital (*Landspítalinn*) in Reykjavik. The latter, with 200 beds, is the largest general hospital in Iceland.

By now I had been almost two hours on my visit, but my host urged me to stop in at his apartment before going back to camp, and I agreed. It was just across the road down the west slope of the fiord — a one-story, white cement structure. As we entered through a small wooden gate, there were four or five young children scampering about the yard. We passed through a doorway into a narrow hall where toys and rubber overshoes were scattered about. There were two apartments, one occupied by Richard *Laeknir*, the other by the superintendent of the sanatorium. The former had just four rooms — a sitting room, bedroom, bathroom and kitchen — in which he, his wife and their one-year-old son, lived. The sitting room was small, yet comfortably furnished; mulberry-colored draperies framed the unusually large and pleasant windows; two striking oil paintings by Kjarval, Iceland's best-known contemporary artist, were tastefully hung on the wall opposite me; both depicted wide stretches of wild, forbidding, lava-strewn land. These paintings had been a gift in which Richard *Laeknir* evidently took pride. We sat down in two armchairs, near several brightly polished brass ornaments, including a huge, flat brass tray with small ash receptacles on it.

A few minutes after our arrival a buxom, smiling young woman entered the room and was introduced to me by Richard *Laeknir* as his wife. She spoke no English, but her cordial expression spoke for her and I knew right away that I was welcomed. She soon withdrew from the room, bowing slightly. From the sounds I shortly began to hear in the adjoining rooms, I knew she was preparing some refreshments. While she was gone, Richard *Laeknir* and I continued our conversation.

Up to 1930 Iceland had had high morbidity and mortality rates in tuberculosis. Both, fortunately, have dropped since then. The highest accurately recorded death rate from all forms of the disease was in 1920, when it was 210 per 100,000. In 1918 it had been 200. In 1929 and in 1932 it was still at this figure, dropping in 1937 to 130, and in 1941 to 80. At present the death rate is 100 per 100,000; since the population now totals 120,000, approximately 120 died last year from this disease.

Tuberculosis is being discovered and treated earlier than it was twenty years ago. Still, many cases are far advanced when the patients first arrive at the sanatoriums. This past year there seems to have been an increase in the incidence of the pulmonary type of the disease, chiefly in adolescents, particularly girls. The overcrowding in some of the larger cities, like Reykjavik, and the increase of measles this year are considered to be possible contributing factors. Also there still remain people who, though obviously ill, procrastinate about seeing a physician. As yet there is no law forcing one to go to a sanatorium unless the person has active (contagious) tuberculosis and lives in proximity to young children and adolescents. Chest roentgenograms are being increasingly utilized on the outside, even in the country districts; in some of the latter, especially where the local morbidity rate of tuberculosis is high, all except the very young have had them. Contacts are always skin-tested; usually the von Pirquet method is first employed; if this test proves positive, the Mantoux is used; if the latter is also positive and the patient is young, chest films are always taken. All patients at Kristnesi are skin-tested.

Tuberculosis in cattle is rare. Bovine-type bacilli are infrequently found, and there is little of the childhood form of the disease. Although most of the cows are not tuberculin-tested, the only milk that is rendered pathogen-free (stassinized — a Swedish method) is available solely in Reykjavik and Akureyri. A dairy farm outside Reykjavik supplies milk from a herd of tuberculin-tested cows for the use of young children.

All autopsies in Iceland are performed, with rare exceptions, by a specially appointed medical officer in Reykjavik. According to this plan, no postmortem examinations may

be carried out by either of the physicians at Kristnesi. An autopsy in a medicolegal case may be performed in any locality by a properly authorized physician. In the ordinary situation the majority of people, unfortunately, refuse to give their permission for an autopsy. When a patient dies at the Kristnesi sanatorium and permission has been obtained to perform an autopsy, the body has to be preserved in some manner, shipped to Reykjavik by boat, a voyage of two to three days, and finally be examined by someone unknown to the family. Under these conditions it is readily seen why not many permissions for autopsy are given. As yet no law exists that allows the performance of an autopsy without this permission.

Toward the conclusion of our talk, Richard *Laeknir* said a few words about two other diseases that in years past were frequent throughout this land — smallpox and leprosy. At present smallpox is nonexistent, chiefly owing, without doubt, to universal vaccination, which long ago was adopted in this country. All persons are vaccinated in their first year, in the fourteenth and at other times as deemed advisable in the individual case. Leprosy was common in the eighteenth century, when the disease, then rife throughout the world, spread to Iceland via (so it is thought) the Baltic States and Norway. Leprosariums were soon established; — the first at Laugarnes pronounced phonetically "Lerr-gar-ness"), just outside Reykjavik. (Laugarnes means "warm fountain near the peninsula"); the second at Kópavægur, about halfway between Reykjavik and Hafnarfjörður. At present there are about 20 cases of leprosy in Iceland.

Distribution of medical care was only sketchily discussed. In contrast to the present situation in the United States, it is largely under the direction of the State. Iceland is divided into fifty-two districts, with a physician assigned to each one. For assuming care of all indigents in his district, this man is paid a salary by the State, varying before the inflation (1941-1944) from 3000 to 4000 *kr.* (prior to 1941 a *krona* was worth 15 cents). The higher salary is obtained in the more sparsely populated districts. The physician is allowed to have private patients, but the latter are comparatively rare, so that his chief source of income is the salary paid him by the State. The position of being a district physician is now not much desired by the men just entering practice. Instead, the majority are eager to take up a specialty in Reykjavik. This poses a serious problem in the distribution of medical care in the near future. The threat of an actual oversupply of physicians in Iceland presents another problem, made more pressing with each passing year. The School of Medicine at the University of Reykjavik has been overcrowded for the past few years and, so far as Richard *Laeknir* knew, there has been no enforced limitation on the number of entering medical students; there has been solely the scholastic requirement to fill. The School of Medicine at present has a total of about sixty students, with about ten to each class. It was his opinion that three or four doctors each year would be sufficient for the needs of Iceland.

By that time his wife had returned with delicious coffee and several kinds of cakes and cookies and had set them out most attractively on a card table on the other side of the room. Richard *Laeknir* and I sat down on two small chairs so that we faced each other. I was surprised that his wife did not sit down with us and also partake of the refreshments, which I wish to repeat were delicious. Later I learned that it is the usual custom for the wife to wait on her husband when he is entertaining a stranger, and not to join in either the conversation or the refreshments.

My visit over, I took my leave, thanking them both as best I could for the truly delightful and interesting time I had had. My driver had just driven up to the outside gate in the ambulance, and soon I was well along the narrow road back to camp.

CAPTAIN T. DENNIE PRATT, M.C., AUS
Iceland

NOTICES

SUFFOLK DISTRICT MEDICAL SOCIETY

The annual meeting of the Suffolk District Medical Society will take place on Wednesday April 26, at 7:30 p.m., at the Hotel Puritan, 390 Commonwealth Avenue, Boston. Dinner will be served in the Crystal Room. Dr. Frank H.

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PAPILLOMATOSIS OF THE LARYNX IN CHILDHOOD*

A Report of Fifteen Cases

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BOSTON

FIFTEEN patients with laryngeal papillomatosis were treated at the Children's Hospital in Boston during the ten-year period 1933-1942. It is the purpose of this paper to review briefly the clinical and pathologic aspects of the disease shown by these cases, with special reference to modes of treatment and results of therapy.

Papillomas are the commonest tumors of the larynx in childhood and should always be seriously considered by the physician in the differential diagnosis of chronic hoarseness. According to Jackson,¹ these tumors are the most frequent of all benign growths occurring in the larynx. In children,

The incidence of laryngeal papilloma as estimated from the literature is approximately 1 case per 1000 clinic patients. During the period covered by the 15 cases here reported, however, 82,644 children were examined in the Out-Patient Department of the hospital, an incidence of approximately 1:6000. Over 200 cases have been treated at Jackson's large bronchoscopic clinic in Philadelphia throughout his many years of service.¹ The disease is allegedly more frequent in males than in females, although in this series 10 patients were girls and only 5 were boys (Table I). It may occur at any age, but its onset is most frequent between eighteen months and four

TABLE 1.

CASE NO.	SEX	AGE AT ONSET	NO. OF TRACHEO-EXCISIONS	TREATMENT OTHER THAN TRACHEO-EXCISION	DURATION OF TREATMENT	DURATION OF DISEASE	CONDITION	END RESULT VOICE	END RESULT LARYNX	DURATION OF FOLLOW-UP
1	F	7 yr	2	Yes	None	1 5/12 yr	2 1/2 yr	Cured	Normal	2 yr
2	F	3 5/12 yr	3	Yes	None	2 yr	1 yr	Dead	Papilloma	
3	F	1 6/12 yr	1	No	None	1 day	1 1/12 yr	Cured	Normal	6 yr
4	F	3 1/12 yr	1	Yes	None	8 mo	3 yr	Cured	Normal	6 yr
5	F	1 9/12 yr	4	No	X-ray	8 mo	1 yr	Cured	Normal	6 yr
6	F	3 6/12 yr	11	Yes	X-ray	3 3/12 yr	4 yr	Cured	Normal	4 yr
7	M	7 mo	4	Yes	None	6 mo	1 5/12 yr	Dead	Papilloma	
8	M	3 6/12 yr	1	No	None	1 day	4 mo	Cured	Normal	6 yr
9	F	5 11/12 yr	2	No	None	3 mo	10 mo	Cured	Normal	1 1/2 yr
10	M	4 mo	15	Yes	X-ray	1 8/12 yr	2 6/12 yr	Cured	Normal	2 yr
11	F	3 yr	20	Yes	None	2 2/12 yr	5 2/12 yr	Dead	Papilloma	
12	M	Birth		No	None			Unchanged	Hoarse	Still under treatment
13	F	4 5/12 yr		No	None			Unchanged	Hoarse	Papilloma Still under treatment
14	F	4 mo		Yes	Amniotic			Unchanged	Hoarse	Papilloma Still under treatment
15	M	4 yr.	34	Yes	None	5 1/2 yr	13 yr	Cured (recurrence)	Hoarse	Under treatment at another hospital

papillomas tend to be multiple and may arise from the vocal cords or the mucous membrane of any other part of the larynx, epiglottis or trachea. They are histologically benign, but, because of extreme rapidity of growth and an extraordinary tendency to local recurrence, coupled with the constant threat of glottic obstruction, their clinical nature is notoriously treacherous. According to Crowe and Breitsstein,² the mortality from laryngeal papilloma in children under five equals and possibly exceeds that of carcinoma of the larynx in adults.

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years. According to Gerhardt,³ about one fifth of all cases are congenital. Only one child in the present series had symptoms dating from birth. In no case was there any familial incidence of the disease.

No conclusions can as yet be drawn concerning the specific etiology of papilloma of the larynx. It has frequently been suggested that a close relation exists between the common cutaneous wart and the histologically similar laryngeal papilloma. Ullmann⁴ in 1923 was apparently able to transplant the growths by means of a filterable agent, both to the skin and to the mucous membranes. The mucosal transplants developed after two or three months of incubation and were identical with the donor papillomas, both grossly and histologically. On the skin, the trans-

plants developed as flat warts, resembling microscopically and grossly the common verruca plana. Ullmann's series was small and poorly controlled, and his work has not been confirmed; nevertheless, it is extremely interesting. That a filterable virus is responsible for this disease is still a possibility.

Chronic laryngeal irritation from recurrent infection, dust and gases was formerly thought to play an etiologic role, but there is no evidence that it is of any

well defined. Varying stages of nuclear degeneration are seen throughout the horny layer.

According to Lipschutz,⁶ inclusion bodies are sometimes found in the epithelial cells of laryngeal papillomas. He describes these as basophilic and intranuclear. A search for inclusions was made in the pathologic material from the Children's Hospital cases, but none were found. The presence of nuclear inclusions presumably adds support to the virus



FIGURE 1. Photomicrograph Showing a Cross Section of the Processes of a Papilloma.

true significance. It is interesting that Jackson¹ saw over 25 cases of adult papilloma in veterans of World War I who had been gassed.

Histopathologically, laryngeal papillomas are distinctly benign neoplasms, with little to suggest a chronic inflammatory process. They consist of pedunculated or sessile processes of proliferated squamous epithelium with a central core of connective tissue and small vessels. They are frequently branched, and peglike projections of epithelium may be seen extending down into the underlying stroma. The cells are well-differentiated, mature epithelial cells, and there is no true invasion of the stroma or extension into the submucosa below the intact, well-defined basement membrane (Figs. 1 and 2).

The cells lining the basement membrane are identical with those of the basal layer of normal laryngeal mucosa and of normal epidermis. They tend to be elongate, with hyperchromatic nuclei. Mitotic figures are extremely rare. Farther out from this basal layer there is a transition to larger, polyhedral cells with clear, vesicular nuclei containing one or more nucleoli. Keratinization of this outer layer is usually

theory of etiology of laryngeal papilloma. Considerable difficulty, however, is encountered in differentiating basophilic intranuclear inclusion bodies and the various forms of nuclear degeneration so frequently seen in the horny layers of a laryngeal papilloma.

The gross appearance of these tumors is characteristic. On laryngoscopic examination they are seen as glistening, grayish-pink or yellowish-pink, mulberry-like masses with a punctate or finely nodular surface that project from the mucosa of the cords, anterior commissure or elsewhere. They vary in size from nodules only a few millimeters in diameter to fungating masses as large as an olive (Fig. 3). There is practically never the appearance of infiltration of the underlying structures or ulceration of the cords, as in carcinoma. Although implantations may occur and local recurrence is the rule, these tumors are always benign, never invading or metastasizing.

In children, the lesions are usually multiple, as opposed to the more frequently single adult form. The vocal cords are the most frequent sites, but the tumors may occur anywhere in the larynx. Often the

anterior commissure is a favorite region of extremely prolific growth. Extension or implantation on the mucosa of the epiglottis, subglottic region or trachea is common, and the lesions have been known to appear in the fauces or buccal cavity and even to

may occur. Stridor and dyspnea develop as the tumors mechanically obstruct the glottic airway.

Laryngeal dyspnea was a fairly late development in these cases, occurring as a rule only after untreated hoarseness had been present for several months.

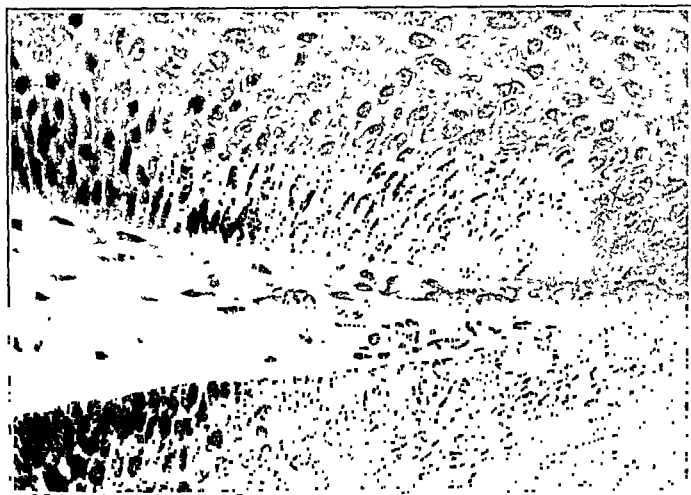


FIGURE 2. Photomicrograph Showing Well-Differentiated Cells and a Well-Defined Basement Membrane.

involve the lips. In this series, palatal and tonsillar implants were discovered and removed.

The symptoms produced by papillomas are in no way different from those of any laryngeal tumor, namely, hoarseness, aphonia, stridulous breathing,

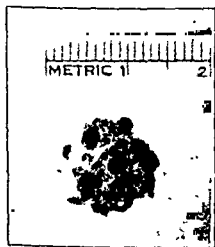


FIGURE 3. Photograph of a Laryngeal Papilloma.

dyspnea and, later on, the resultant signs of increasing laryngeal obstruction. Of these, progressive hoarseness is the most frequent presenting complaint, but exists only when the tumor interferes with the vibration, approximation or tension of the vocal cords. Loss of voice to the point of complete aphonia

There are notable exceptions, however, when laryngeal obstruction develops early and acutely, as a polypoid tumor mass is prolapsed or sucked into the glottis, necessitating emergency tracheotomy. This occurred in a patient who had been given ether anesthesia preparatory to direct laryngoscopy, and an emergency tracheotomy had to be done. Laryngoscopy revealed a pedunculated, olive-sized mass that had prolapsed into the glottis and was firmly impacted between the two cords. In retrospect, it was probably unwise to have given this patient a general anesthetic, even though she had manifested only the mildest signs of laryngeal obstruction. Our policy has since been to use no anesthesia when even the slightest suggestion of respiratory difficulty is present. Cough is occasionally present, but was a minor symptom in these cases. When a large mass of tumor projects upward from the larynx, dysphagia may occur.

The diagnosis of papilloma of the larynx can be made only by laryngeal examination, and in children direct laryngoscopy is almost always necessary to accomplish this. Lateral roentgenograms of the neck, especially laminagraphs, are occasionally helpful. Biopsy should be performed in all cases, although this procedure is much more important in adults than in children, since in the latter carcinoma of the larynx

is so rare as to be practically unheard of and the clinical appearance of the papilloma is most characteristic. The physician who is confronted with the problem of progressive hoarseness in an infant or child must consider many diseases in differential diagnosis. The most frequent of these are papilloma or some other benign tumor, a foreign body, chronic laryngitis associated with sinusitis, syphilis or tuberculosis, so-called "screamers' nodes," laryngotracheitis, malformations, congenital webs, recurrent paralyses, hypertrophic ventricular bands and so-called "laryngomalacia." No definite diagnosis can be conclusively made without direct laryngoscopy, and the importance of carrying out this procedure without delay cannot be overemphasized.

Papillomas of the larynx in childhood are always benign, and the disease is almost always self-limited. These two basic premises dictate that treatment be as conservative as possible. If the delicate structure of the larynx is preserved intact with no operative or irradiational injury to normal tissue, the papillomas eventually cease to recur and the child regains a normal larynx and a normal voice. As a rule, after removal the tumors recur with great persistence, but they usually disappear spontaneously after a few years, regardless of treatment. There seems to be an activity phase of these growths during which repullulation occurs consistently until the process is "burned out." This has been called by Broyles⁶ the "juvenile phase." Following this, the tumors may persist indefinitely without treatment, but excision at such a time usually results in a permanent cure. In this phase of relative inactivity papillomatosis in children resembles the adult form of the disease, which can usually be permanently cured by a single excision.

The average duration of the disease in the present series was three years. Three patients are still under treatment, and 2 of these have had symptoms for five and eight years, respectively. The briefest course of the disease was in a boy of three years of age who had had symptoms for eight months and was cured by a single endolaryngeal excision. Remarkable cases are reported in the literature in which the disease persisted for twenty or thirty years. In Lejeune's⁷ case, the papilloma persisted for twenty-one years, despite all forms of treatment, including ninety-seven operative procedures, finally terminating fatally with the development of squamous carcinoma of the larynx.

The variety of therapeutic measures advocated by different authors in the treatment of laryngeal papilloma is strong evidence of the uniform lack of consistent success of any single mode of therapy now available. Various medicinal measures have been advised. Most of these consist of the local application of absolute alcohol, zinc chloride, silver nitrate, iodine, salicylates, acid nitrate of mercury, nitric acid or other escharotics. *Thuja occidentalis*, potassium iodide and particularly calcined magnesia have been used systemically. In the judgment of writers,

none of these medicinals have any effect on the course of the disease. We have had no experience with them.

Broyles⁶ at the Johns Hopkins Hospital has recently reported 5 cases treated locally with an estrogenic hormone preparation (Amniotin). The rationale of this therapy was based on the well-known tendency of laryngeal papillomas in children to disappear spontaneously at, or just before, puberty, and on the fact that local applications of estrogenic hormones to the vaginal mucosa of prepubescent girls produce a change from the childhood to the adult type of epithelium. Such changes in the laryngeal mucosa, however, have not been demonstrated, although alterations in the voice at puberty in both sexes are self-evident. The results in Broyles's series were not convincing, in that in each case the disease had existed for many months before the beginning of treatment and an apparent cure was obtained only after the continued use of estrogens for four to eight months; in other words, success was attained at about the usual period in the course of the disease when spontaneous remission might be expected. One of our patients was given a course of local estrogen therapy, Amniotin in oil in 1-cc. (10,000-unit) doses being applied to the papillomas and adjacent laryngeal mucosa once weekly for seven months, with no detectable change in the rate or character of the growths, grossly or histologically. In our opinion, the efficacy of this method of treatment, applied in such a small number of cases, is as yet unproved.

Radical operative procedures, such as laryngofissure or thyrotomy, were formerly used in treatment of papilloma of the larynx. These methods are to be wholeheartedly condemned in view of the benign nature of the disease and the laryngeal stenosis and permanent laryngeal damage that usually develop in children following the use of these radical surgical methods.

Mackenzie⁸ in 1901 first advocated the use of tracheotomy and expectant treatment in cases of papilloma. The rationale was to provide an adequate airway and to keep the larynx at rest until the tumors spontaneously disappeared. Clark⁹ in Boston in 1905 reported 14 cases treated in this manner, and pointed out that if the tumors persist after the age of puberty in a tracheotomized patient, endolaryngeal excision is most apt to result in success, since the tumors have then usually passed out of the phase of activity. In our opinion, tracheotomy is not necessary unless signs of laryngeal obstruction persist, or unless the patient cannot be kept under relatively close observation. The care of a tracheotomized child at home is always a problem, and it often proves difficult for the mother to manage the changing of tubes, maintain adequate cleanliness and exercise constant supervision. One of our patients died of asphyxia at home as a result of his removal of the tube without the mother's knowledge.

Irradiation of the growths by x-ray or radium has had considerable success in the hands of several authors. New,¹⁰ of the Mayo Clinic, advocated the use of radium endolaryngeally and externally. This method was also supported by Crowe² at the Johns Hopkins Hospital. Foster¹¹ in 1933 reported 3 cases treated with x-rays. Although in some cases radiation therapy apparently results in cure of papillomas, the danger of irreparable damage to the delicate laryngeal cartilages is great enough to condemn this method of treating benign, self-limited tumors. Necrosis may easily be produced in the highly sensitive, growing cartilages of the larynx in children. It is also possible that external irradiation of the larynx will have some untoward effect on the thyroid gland of a growing child. Jackson¹² reports that he has never seen a cure of papilloma of the larynx that could be attributed to x-ray therapy.

Fulguration of the growths by the endolaryngeal application of diathermy or cautery has been frequently used in some clinics, but the resulting damage to the cords and laryngeal cartilages makes its use unwarranted. Moreover, as Jackson¹ points out, recurring papillomas of the larynx constitute a repullulation from the surface epithelium, and nothing is to be gained by cauterization of the base of each tumor. Another independent lesion often develops elsewhere along the mucosal surface.

At the Children's Hospital, the method of choice in treatment of laryngeal papillomas is that of repeated endolaryngeal excision. This is accomplished in most cases by direct laryngoscopy under general anesthesia with Avertin (80 to 100 mg. per kilogram of body weight), supplemented by ether. The tumors are gently removed with biting forceps repeatedly applied. A twisting motion of the wrist cuts off the tumors flush with the adjacent mucosal surface and leaves the basement membrane of the underlying mucosa intact. No resistance is usually encountered unless one has made the error of grasping normal tissue. The anterior-commissure laryngoscope is also employed to gain free access to the subglottic region as well as the anterior commissure. Suspension laryngoscopy is neither necessary nor advisable.

Tracheotomy is done at this hospital only when dyspnea or signs of laryngeal obstruction exist, being otherwise avoided. It was employed in 9 of the 15 patients in this series, but in none of the more recent ones. An effort is made to examine the patients under treatment every two to four weeks, and excisions are carried out as often as recurrence demands. This method of repeated excision is not suggested as a specific means of cure, since in practically all cases these growths tend to recur; but when it is performed at sufficiently frequent intervals, an excellent airway is constantly maintained, without the necessity and added risk of a temporary tracheotomy. In 6 cases, only a few

excisions at intervals of three to six months were necessary for permanent cure. In 3 others, a single excision sufficed. In the remaining 6 cases, however, excisions were necessary as often as every two to four weeks, with an occasional respite of one to two months, the periods of therapy averaging two years. A patient who is still under treatment has had thirty-five excisions during the course of five years.

Three patients received brief courses of x-ray therapy in addition to endolaryngeal excision. In no case was any improvement obtained, and in 1 case actual stimulation of growth seemed to result. As mentioned above, 1 case was treated with local estrogenic hormone after the method of Broyles,⁵ with no change in the rate or character of the growths after six to seven months of weekly applications. Multiple excisions have since been necessary.

Three patients died while under treatment, but only one of these deaths can be directly attributed to the papilloma. This fatality occurred in a child who died suddenly of asphyxia at home shortly before the appointed time for a readmission for excision. Death apparently resulted from prolapse of a mass of papilloma into the glottis, causing sudden strangulation. In the second case, mentioned above, death resulted from asphyxia when a two-year-old baby pulled out his tracheotomy tube at home. The third patient died at another hospital of laryngeal diphtheria.

Three patients are still under treatment, and a fourth, who was under treatment for over six years, having undergone thirty-eight endolaryngeal excisions, was recently found to have recurrent papilloma. This patient, now seventeen years old, was recently called back for examination five years after the last excision. A laryngoscopy and bronchoscopy performed three months after the last excision had been negative, and the patient had been discharged because he had reached the hospital's age limit of twelve years. He had been asymptomatic and had consequently not bothered with follow-up examinations in an adult clinic, to which his case had been referred at discharge. Excision of the papillomas at the present time will probably result in permanent cure, since the phase of activity has most likely passed.

Eight cases were cured by endolaryngeal excision. In each of these the voice and larynx are normal and no complications resulting from treatment exist. No recurrences have occurred in follow-ups ranging from one and a half to six years.

SUMMARY

Fifteen cases of papilloma of the larynx in childhood are reported.

Papillomas are the commonest tumors of the larynx in childhood, and are benign, self-limited growths that tend to recur but also to disappear at puberty.

The etiology of the disease is unknown.

The diagnosis should be suspected in any case of progressive hoarseness in a child, and direct laryngoscopy should always be performed.

The recommended treatment is repeated, careful superficial excision, with tracheotomy reserved for those cases with severe laryngeal obstruction or for cases that cannot be kept under frequent observation. Radical surgical methods are condemned. Radium or x-ray therapy is not without danger.

Of the 15 reported cases, 8 show excellent clinical cures, each patient having a normal voice and a normal larynx. Three patients are still under treatment, and only 1, who was discharged as normal five years ago and is now seventeen years of age, has had a recurrence. Three patients died, 2 as a result of asphyxia at home and 1 of laryngeal

diphtheria. Only 1 of these deaths was directly attributable to the papilloma.

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CAUSALGIA AND GANGRENE: RARE COMPLICATIONS IN MENINGOCOCCAL MENINGITIS*

Report of a Case

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IN the enormous recent literature dealing with meningococcal meningitis, no reference to skin and toe gangrene terminating in spontaneous amputation nor to the more unusual syndrome of causalgia has been observed. In the case reported below, these conditions became manifest after the initial fulminating attack subsided, and caused protraction of disability for four months. That there was a common etiologic basis for these pathologic changes is uncertain and difficult to maintain. Their rarity in this disease, the uncontrollable and intractable pain, the extended period of illness and the ultimate loss of body members are sufficiently noteworthy to warrant a brief report.

REPORT OF CASE

M. H., a 34-year-old woman, was admitted to the Newport Hospital, on January 31, 1943. She had been up and about with a "head cold" for a few days, until chills, severe pains in the extremities and back, and moderate fever set in. On the sudden appearance of diffuse purpuric skin lesions and a stiff neck, she was admitted to the hospital.

Between 1929 and 1937 the appendix, internal genitalia and gall bladder were removed and a nephrotomy for kidney abscess was performed. In 1939, the patient had a "nervous breakdown." Except for an underlying anxiety psychosis, there were no illnesses except those treated surgically. The menopause was operatively induced in 1935;

prior to that time, the menses were normal. There had been no pregnancy.

Physical examination showed a confused, transiently irrational patient who repeatedly demanded relief from excruciating pain in the head, trunk muscles and extremities. The skin was cold and clammy, and the limbs were severely painful, stiff, cold and numb. There was marked spasm of the neck and back muscles, and the knee, ankle, wrist and elbow reflexes were hyperactive. The Babinski sign was equivocal. No lid ptosis, squint, nystagmus, facial paralysis or optic neuritis was found. There was no incontinence. The head and neck revealed no other abnormalities except injection and reddening of the pharynx, uvula and tonsillar tissue. The heart and lungs were normal. Except for a well healed suprapubic scar and skin hyperesthesia, the abdomen revealed no unusual signs. A pelvic examination was not performed.

The skin contained numerous huge, irregular, moderately indurated purpuric areas, among which were petechial hemorrhages ranging from those of minute size to coalescent groups or patches 2 to 5 cm. in diameter. Except for the face and hands, these were scattered over all parts of the body—especially on the thighs, neck and extremities. On the dorsum of each foot was an area of purpura involving the central toe and a space 2 cm. proximal to them; this was well demarcate and leathery and so painful that contact with bed sheets was unbearable.

The temperature was 99°F., the pulse 100, and the respirations 20. The blood pressure was 110/60. The white-cell count was 19,600, with 84 per cent polymorphonuclear leukocytes and 16 per cent lymphocytes. The red-cell count was 5,000,000, the hemoglobin 90 per cent, and the color index 0.8. The urine was normal, and a Kahn test was negative.

Spinal puncture yielded 25 cc. of thick yellow fluid under increased pressure. The white-cell count of the fluid was 670, the globulin level + + + +, and the sugar level slightly below normal. A direct smear revealed many gram-negative biscuit-shaped extracellular diplococci. A spinal tap on the following day revealed a white-cell count of 5100, and the direct smear showed the same findings as the previous one.

On the 2nd hospital day, a deep cyanosis of the mucous membranes appeared after 90 gr. of sulfadiazine had been

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given. The sulfadiazine level in the blood was 3.9 mg. per 100 cc. Halving the daily dosage of sulfadiazine during the next three days reduced the blood level to a negligible quantity. At no time was there leukopenia or secondary anemia. During the first 10 days of the disease the excruciating pain, generalized purpuric eruptions and disturbances of the sensorium dominated the clinical picture. Satisfactory relief was unobtainable with large doses of opiates, and at no time was there complete freedom from pain. Vitamin B₁, glucose and physiologic saline solution were administered intravenously daily to supplement the limited diet.

On the 6th day, the patient complained of a jump in the throat, dysphagia and pharyngeal soreness. There was no choking sensation. Examination failed to reveal a cause for these complaints. By that time the painful, indurated purpura of the toes had become gangrenous and well demarcated, and there, as in several larger areas of ecchymosis on the trunk, thighs and legs, a generalized sloughing began. Daily débridement maintained free drainage, and after this the hitherto elevated temperature (102 to 104°F.) subsided and remained normal. Caudal anesthesia induced by a mixture of 30 cc. of 1 per cent novocain and 70 cc. of physiologic saline solution did not relieve the severe pain in the feet. This pain, in fact, did not completely disappear until the 75th day, when the gangrenous members — the 2nd, 3rd, and 4th toes of the right foot and the 2nd and 3rd toes of the left foot — were surgically disarticulated at the metatarsophalangeal joints. At that time, the lesions of the thighs, trunk and legs had entirely healed and large, indurated, reddish-brown scars had replaced the sloughed purpuric areas of skin. Heat-cradle therapy, whirlpool baths and massage were employed for restitution of function of the lower extremities.

Throughout the hospital stay, the disturbances described above were continuously complicated and enhanced by a painful lesion in the right arm and hand, which followed a causalgia pattern. During the first week, cyanosis, numbness and coldness were followed by hyperesthesia, tingling and hot sensations and an incessant throbbing pain. The extremity became edematous, and the moderately cyanotic skin assumed a glassy and translucent appearance and a putty shade. The fingers and hand became puffy, and continued to tingle with an intermittent burning pain superimposed on a constant sensation of aching soreness. The slightest vibration or motion aggravated the pain. Two palmar blocks with 20 cc. of 1 per cent novocain, analgesics, somnifacients and opiates in huge doses failed to furnish any relief. There was never any evidence of abnormal vascular pulsations or thrombosis.

The constant suffering, insomnia and mental anguish of the patient caused by the pain in the right arm were reflected in her debilitated and cachectic appearance. The excruciating pain seemed at all times out of proportion to the visible changes in the extremity. It confined itself solely to the course of the ulnar nerve, descending from the medial aspect of the arm, where it remained for 36 days, into the area above the styloid process of the ulna bone, where it persisted for 40 days, and thence into the palm and the 4th and 5th fingers. On the 100th day, the pain disappeared.

Long immobilization caused atrophy of disuse, cyanosis, edema and hirsutism and markedly altered the appearance of the involved limb. That profound trophic changes had taken place was indicated by an x-ray film taken prior to discharge on the 120th day. General osteoporosis, particularly in the extremities of the bones rather than the shafts, was observed, and there was also new destruction of the cortex and cartilage.

DISCUSSION

Gangrene of the toes and also lesions involving large areas of the skin are rare complications of meningococcal cerebromeningitis. In the present case, their coincident appearance and the simultaneous necrosis, sloughing and healing indicate a

common etiologic factor. No stained slides demonstrating meningococci, however, were made from either the skin or toe lesions. The cause was probably a trophic disturbance based on a common, widespread vascular lesion, produced by a peripheral thrombosis — embolic or autochthonous — or by a peripheral vasospasm from an exotoxin.

The pain associated with the gangrene was probably due to peripheral neuritis, secondary to nutritional changes in the surrounding tissues affected by vascular lesions, and the intensity of pain varied proportionately with the degree of necrobiosis, disappearing finally after complete disarticulation. Pain accompanying gangrene is not uncommon.

The syndrome in the right arm may properly be attributed to causalgia, a rare and bizarre clinical picture of pain without visible lesions, thought to be due to vascular, neurogenic or psychic phenomena. The presence of all the latter phenomena and the absence of demonstrable primary tissue changes satisfactorily explain the intense and constant pain in the right arm and hand. Had the pain been due to a vascular lesion alone, its prolonged duration and marked severity would have been accompanied by tissue changes more profound than actually existed. Had it been occasioned by hysteria or psychoneurosis alone — and these were undeniably present — it would be difficult to explain the moderate tissue changes as well as the selective reference of pain, completely and at all times, to the course of the ulnar nerve. That the cause was a neuritis due to a vascular disturbance — toxic, embolic or thrombotic — in the nutrient vessel of the nerve itself seems to be the most satisfactory explanation even though it is extremely difficult to prove. Thus the paradox of severe pain in the arm and hand associated with only minor pathologic changes, and the uncertainty whether the etiologic factor was neurogenic, vascular or psychic, warrant a diagnosis of causalgia.

SUMMARY

A case of cerebrospinal meningococcal meningitis is recorded because of two rare complications, purpuric dry gangrene of the toes and of scattered areas of the skin and causalgia of the right upper extremity. The important aspects of these complications were the prolonged duration of the disease, the loss of body structures because of necrosis and the uncontrollable pain. The emboli that probably caused these phenomena were of profound clinical significance because of the possibility of their fortuitous destination in vital areas of the body — brain, heart and lungs. The prognosis was therefore guarded.

CLINICAL NOTE

VOMITING OF AN OPEN SAFETY PIN¹

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BOSTON

THE successful vomiting of an open safety pin is such a rare occurrence that the reporting of such a case seems justifiable. Only 3 similar cases have been found in the literature. In 1909, Good-



FIGURE 1. Roentgenogram Showing the Safety Pin in the Stomach.

man¹ reported a case in which an open brooch 6 cm. long was swallowed by an eight-month-old baby and vomited fifteen weeks later. In 1916, Earp² reported the case of an eight-month-old baby who vomited an open safety pin 5 cm. in length. In both these cases, however, there was no x-ray or other proof that the safety pin ever reached the stomach, and the size of the pin as compared with the size of

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the child makes these accounts seem doubtful. In 1927, Orton³ reported the spontaneous expulsion of an open safety pin from the stomach by a seven-month-old baby, who expelled it into the esophagus within one week after swallowing it (confirmed by x-ray examination, and as arrangements were being made for an esophagoscopy regurgitated it from the esophagus into his mother's hand. The size of the pin was not recorded.

REPORT OF CASE

R. S. (M.G.H. U-381630), a 3-year-old girl, entered the Emergency Ward of the Massachusetts General Hospital on November 9, 1943, having swallowed an open safety pin a few minutes before entry.

Physical examination showed a child in no distress, with no abdominal tenderness and normal temperature, pulse and respirations

X-ray examination (Fig. 1) revealed a medium-sized open safety pin in the stomach, with the point slightly bent toward the keeper. I advised keeping the patient in the hospital a day or two, expecting that the pin would be passed through

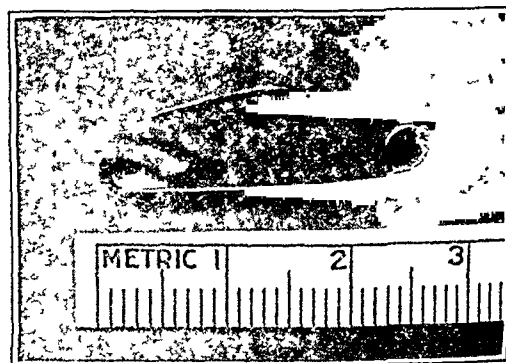


FIGURE 2. Photograph of the Safety Pin.

the intestinal tract without difficulty. A few hours later however, the patient vomited and the pin was recovered (Fig. 2). It measured 2.7 cm. in length

Except for an attack of vomiting (without hematemesis) the day after the expulsion, the patient had no further symptoms.

The whole episode took place within a 5-hour period. The fact that the point was bent toward the keeper must have facilitated the swallowing and subsequent vomiting.

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Correction: In the paper "Meningitis in Children," by Drs. Charles H. Hollis and James Marvin Baty, which appeared in the March 9 issue of the *Journal*, the figure "15,000" in column 1, line 52, on page 280 should be "1500."

MEDICAL PROGRESS

INHALATION THERAPY (Concluded)*

MAURICE S. SEGAL, M.D.†

POSITIVE-PRESSURE THERAPY

The use of positive-pressure therapy, as a rule employing a mixture of oxygen and helium, has not become so widespread as it should be. It is indicated in the treatment of various types of pulmonary edema, bronchial asthma and obstructive respiratory disease.

Physiological Basis and Clinical Application

Barach and his associates¹³¹⁻¹³⁵ established the clinical application and usefulness of positive pressure and the physiologic factors involved in the treatment of obstructive dyspnea and acute pulmonary edema. They devised two types of apparatus, of which one provided positive pressure during both phases of the respiratory cycle,^{9,10} and the other provided it during expiration alone.¹⁶ The signs of pulmonary edema rapidly disappeared, and remained absent so long as the pressure was applied or until the original cause was removed. The application of a gentle internal distending force served to keep the bronchioles patent and opposed the hydrostatic pressure within the capillaries. Barach compared this process with that of putting a finger on the capillary wall itself. He demonstrated by its use a reduction of the negative intrapleural pressure and frequently a lowering of the total pulmonary ventilation. Other modifications in circulatory function were reported, such as an increase in venous pressure that maintains the return of blood to the right side of the heart and a prolongation of circulation time, especially marked in congestive failure. These modifications tended to prevent overfilling of the heart and acted similarly to the application of a tourniquet to the extremities. There was also x-ray evidence of narrowing of the transverse cardiac diameter by the application of high mask pressures.

Positive pressure can be effectively administered through the Barach-Eckman-Molomut mask, which is metered for positive pressures up to 4 cm. of water in the expiratory phase only, or in the hood apparatus during both inspiration and expiration. The patient can be kept in the hood or mask with proper humidification for as many days as necessary. When the need for positive pressure no longer exists, the mask can be used without employing the metered disk for positive pressure and the desired percentages

of oxygen can be given, or the patient may be transferred to a tent if this is considered more desirable. The percentages of oxygen may be gradually lowered before the complete cessation of treatment in order to prevent the recurrence of anoxia. Cerebral and cardiorespiratory symptoms may follow the sudden stopping of oxygen therapy in cases of chronic anoxia.

Generally, positive pressures of 2 to 6 cm. of water are sufficient for preventing or treating pulmonary edema. Pressures above 6 cm. may diminish the return flow of blood to the right side of the heart. In some cases higher pressures may be found necessary for short periods. Theoretically, shock may be considered a contraindication to the use of positive pressure. No difficulty need be encountered, however, if low pressures are used, beginning with a pressure of 2 cm. of water and cautiously increasing it as needed.

Anesthesia for Thoracic Surgery

There are essentially no dangers associated with the proper use of positive-pressure therapy of 2 to 6 cm. of water as described above. Anesthetists and thoracic surgeons have employed positive-pressure anesthesia with an intratracheal catheter or closed face mask. The maintenance of sufficient lung function and controlled respiration during a surgical pneumothorax may be obtained by the use of proper mixtures of anesthetic agents under sufficient pressure. The accompanying hazards and disadvantages have been described by Bradshaw,¹⁴⁶ Heidrick et al.,¹⁴⁷ Marcotte et al.¹⁴⁸ and others. Bradshaw reported a case of mediastinal emphysema, and Adams¹⁴⁹ and Heidrick et al.¹⁴⁷ several cases of emphysema. Adams¹⁴⁹ described a case of mediastinal emphysema and subcutaneous emphysema of the neck and face following an asthmatic attack with severe coughing. He stressed the importance of properly controlled low positive pressures and discussed his experimental data, concluding that intrabronchial pressures of 52 to 58 mm. of mercury were necessary to produce a rupture of the visceral pleura. Much lower pressures were needed to produce a rupture of the alveolar walls. These experiments substantiated the previous reports by Coryllos¹⁵⁰ and Macklin,¹⁵¹ and should stimulate interest in the dangers of manipulating the anesthesia bag too vigorously or too often. Adams¹⁴⁹ stated that the intrabronchial pressure may rise as high as 25 to 30 mm. of mercury with a single squeeze of the

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bag. This corresponded to Barach's⁷⁸ demonstration in a tracheotomized patient that a forceful grunt developed a pressure as high as 30 cm. of water. These disadvantages were overcome by Crafoord.¹⁵² He described a new continuously flowing gas-anesthesia machine provided with means for mechanically controlled, automatized respiration. He reported no injuries to the lungs in a large series in which pressures up to 20 cm. of water were employed. These pressures were considerably higher than those commonly employed for the management of pulmonary edema or bronchial asthma in man.

Obstructive and Asthmatic Dyspnea

Barach^{108, 153, 154} summarized the sequence of events that follows resistance of obstruction to inspiration. There is at first a rapid and progressive increase in the intrapleural negative pressure in order to pull sufficient air into the lung. The resistance of the pulmonary bed is lessened and there is at first an increase in the pulmonary blood flow. As the intrathoracic negative pressure mounts, blood continues to enter the lungs through the right ventricle, but the passage of blood through the lungs into the left auricle and from the left ventricle into the extrathoracic aorta is hindered by the high negative pressure within the chest. A progressive accumulation of blood in the lung follows, with a consequent increase in capillary blood pressure. The physical effect of a pathologically elevated negative pressure within the chest is to exert a direct suction action on the pulmonary capillaries, thus tending to cause exudation of serum. The progressive increase in congestion and edema of the lungs requires increased effort for pulmonary ventilation, which in turn manifests itself as an increase in intrapleural negative pressure with the production of additional congestion and edema. The diffusion of oxygen through the swollen pulmonary membrane is diminished. Irregular ventilation through partially obstructed bronchioles increases the anoxia. The rapid, shallow breathing of itself promotes anoxemia, and progressive oxygen want becomes an additional factor as a stimulant to respiration and as a cause of final respiratory failure. The production of pulmonary edema is furthered by anoxemia, which has been shown by Landis¹⁵⁵ to increase capillary permeability.

Barach, Martin and Eckman^{142, 143} demonstrated, both clinically and experimentally, lowering of the intrapleural negative pressure in the lungs by the breathing of therapeutic gases under positive pressure. When the lung was expanded by positive pressure from the atmosphere, a reduced suction pressure was required during inspiration. Helium with oxygen decreased the effort necessary for pulmonary ventilation, thus lowering the negative intrapleural pressure. Macklin¹⁵⁶ demonstrated that normally in addition to the inspiratory elongation

of the bronchial tree, the bronchioles and smaller bronchi dilate during inspiration and constrict during expiration. Barach first observed that a severe asthmatic patient was benefited by pursing his lips during expiration. This led to Barach and Swenson's¹⁴⁴ work. They used lipiodol and conclusively demonstrated a relative increase in the diameters of the small bronchi during the expiratory cycle under positive pressure, which were 25 per cent more open with positive pressure. The positive pressure acted as an internal distending force tending to diminish the constriction of the bronchioles during expiration.

In asthmatic dyspnea the expiratory phase is prolonged owing to bronchial constriction. In obstructive dyspnea the intrapleural negative pressure is increased during inspiration. When air or oxygen mixtures are breathed under positive pressures, the abnormally elevated negative intrapleural pressure is diminished and the dyspnea is alleviated. Barach⁷⁸ pointed out that Nature provides a helpful internal mechanism in the expiratory grunt of the patient with lobar pneumonia and in the pursed lips of the asthmatic patient during expiration. The expiratory grunt maintains a more patent airway and opposes pulmonary edema.

Pulmonary Edema of Varied Etiology

Barach⁷⁸ in a recent paper once again demonstrated, in 5 patients critically ill with pneumonia, the value of properly directed positive-pressure inhalation therapy. He concluded that positive pressure is useful in the treatment of pulmonary edema due to increased hydrostatic pressure and anoxia, as seen in heart failure, or to changes in permeability of the pulmonary capillaries, as seen in pneumonia or gas poisoning. Barach offers a lucid explanation for the mechanism of pulmonary edema occasionally observed in patients with severe pulmonary edema receiving morphine. Lessening of respiratory effort produces a sudden withdrawal of back pressure (positive pressure) on the pulmonary capillaries. This possibility should be entertained in all cases of serious respiratory disease with increased total pulmonary ventilation before using morphine in repeated or large doses. Bookhamer and Cullen¹⁵⁷ successfully controlled 2 cases of pulmonary edema during anesthesia by intermittent pharyngeal suction and the administration of 100 per cent oxygen under intrapulmonic pressures not exceeding 15 cm. of water.

Carlisle¹⁵⁸ successfully employed positive-pressure therapy in the management of 316 cases of pulmonary edema secondary to exposure to industrial gases, without a single fatality. Barach¹⁵⁹ in his most recent paper once again stressed the value of positive pressure in industrial and war gas poisoning. Blankenhorn¹⁶⁰ stated that oxygen under positive pressure is the best method for managing the

pulmonary edema of gas irritation. Observations in a few patients injured in the Coconut Grove fire in Boston thoroughly convinced me⁷² of its value.

In sudden disasters, when positive-pressure therapy is needed for a large group of people, the temporary procedure of instructing the patient to breathe out through pursed lips may be helpful. Short pieces of rubber tubing with lumens narrower than the human trachea can also be distributed, with instructions to exhale through the tubes. It would be of considerable advantage to the armed forces if the routine gas masks were metered for positive pressure in expiration as is the Barach-Eckman-Molomot mask. In this way if a victim inhaled an irritant gas, he could begin positive-pressure therapy before adequate medical help reached him. Such measures as the above are temporary but may be helpful until proper mask equipment is available.

Tracheotomized Patients

Barach and his associates^{142, 145, 161} demonstrated the value of positive-pressure therapy in expiration in tracheotomized patients. Moore and Binger^{142, 163} previously observed this value experimentally. The pulmonary capillaries become accustomed during expiration to a certain positive pressure, and when this is abruptly withdrawn, as in the tracheotomy patient, an increase in capillary permeability takes place, not only in the alveolar capillaries but also in the secreting glands of the tracheobronchial tree. Oozing of serum and mucus follows.

Woodman¹⁶⁴ showed that breathing against positive pressure during expiration in tracheotomized patients results in the successful management of the profuse edema fluid. He believes this to be due to a carbon dioxide effect. Kernan and Barach¹⁴⁵ confirmed this finding. They easily controlled the clearance of serous and mucous fluid in the tracheobronchial tree by having the patient expire through an elongated tracheotomy tube into a water bottle providing a pressure of 3 to 5 cm. Barach¹⁵⁴ outlined the sequence of events in the production of pulmonary congestion and edema in tracheal stenosis. He demonstrated the reversibility of the increasing intrathoracic negative pressures in respiratory obstruction with the use of positive pressures.

In the victim of gas-inhalation, the involvement is largely pulmonary and the proper program to prevent pulmonary edema should be begun at once. The mortality rate in tracheotomized cases of this type is generally high. If tracheotomy must be performed, one should be prepared to keep the opening dry and clear and to apply positive-pressure inhalation therapy with proper humidification through the tracheal cannula.

In general, then, it is best to attempt a program of positive pressure, preferably with a rebreathing hood apparatus, using mixtures of helium and oxygen, before resorting to tracheotomy in cases of

tracheal obstruction, whatever the cause. The number of tracheotomies can in this way be minimized.

Clinical Observations

In employing positive-pressure therapy certain clinical observations are worthy of mention. Many patients find such therapy tiring when the mask is used, and an occasional semiconscious patient at first becomes alarmed at the seemingly increased resistance in the expiratory phase. Reassurance and rest periods can largely overcome this apprehension. When a rebreathing hood is employed, the positive pressure is effective in both inspiration and expiration and the above difficulties do not exist. In the patient desperately ill with serious respiratory disease it is advisable to use either Wangenstein drainage or a Miller-Abbott tube for feeding and decompression, along with positive pressure whenever indicated. The latter can be introduced either through the mask or sleeve of the hood apparatus; it adds materially to the comfort of the patient and enhances his care. I have not observed gastric distention resulting from positive pressure. Free productive coughing and free belching may be somewhat inhibited if therapy is continuous. Positive-pressure therapy should be intermittent, with rest periods of varying time depending on the degree of underlying pulmonary edema. In 2 recently autopsied cases, there were no deleterious effects in the lungs from positive-pressure therapy with pressures up to 4 cm. of water carried on intermittently over periods of two and nine days, respectively.

USE OF HELIUM AND OF HELIUM-AND-OXYGEN MIXTURES

During the last twenty-five years the cost of helium has dropped from \$2500 to 1 cent per cubic foot. The main source of supply is the government-owned Amarillo Field in Texas. Its present volume of production is adequate for its use in the flotation of airships, in medical therapy, for the prevention and treatment of compressed-air illness and in deep-sea diving.

Obstructive Respiratory Disease

Barach made the pioneer observations on the therapeutic use of helium-and-oxygen mixtures. In a series of papers from 1934 through 1944, he described the physiologic basis of its therapeutic value. In 1934, he¹⁶⁵ showed that animals remained well for periods as long as forty days in atmospheres from which all the rare gases had been removed. He also kept mice in sealed chambers in atmospheres of 21 per cent oxygen and 79 per cent helium for periods of two and a half months without harm. He thus proved that rare gases are not necessary for life and confirmed the biologic inertness of helium. Immediately following this, he¹⁶⁶⁻¹⁶⁸ suggested that helium-and-oxygen mixtures be used in conditions

in which there is resistance to the movement of an adequate volume of air to and from the lungs in any part of the respiratory system — namely, bronchial asthma, obstructive lesions of the trachea, larynx and bronchi, emphysema, bronchiectasis and pulmonary fibrosis.

The rationale for the use of helium-and-oxygen mixtures in obstructive respiratory disease rests on the decreased specific gravity of such mixtures and on the fact that the pressure or effort required for the movement of a mixture of 80 per cent helium and 20 per cent oxygen mixture is about half that required for air through similar orifices. In other words, a lighter-than-air mixture flows more easily through a constricted orifice than does ordinary air. During quiet breathing these influences are negligible. With obstruction to respiration, however, an increased negative pressure within the chest becomes necessary for the inward movement of air past the obstruction. Barach demonstrated that it should be possible with helium-and-oxygen mixtures to compensate for approximately a 50 per cent constriction in the lumen of the tubal respiratory tract. The more localized the obstruction the better is the effect, since the viscosity of helium is slightly higher than that of nitrogen. Furthermore, the helium acts as a diluent and vehicle for the oxygen and passes through the constricted orifices to the alveolar sacs.

The percentage of helium and oxygen in the mixture depends on the factors of anoxia and mechanical obstruction. At least 20 per cent oxygen must be used. It is doubtful that helium is of much value if the mixture contains more than 35 per cent oxygen. The Barach rebreathing hood apparatus is the most efficient one for such therapy, but either the Barach metered mask or the B.L.B. apparatus may be used.

The sequence of events that follows resistance or obstruction to inspiration has been summarized by Barach.¹⁵⁴ The resultant pathologically elevated intrapleural negative pressure, pulmonary congestion and interference with left auricular filling and

mann,¹⁷⁷ and Metz.¹⁷⁸ Barach's observations have been confirmed in a series of patients with severe bronchial asthma, gas poisoning, pulmonary edema, atypical pneumonia and postoperative obstructive respiratory disease.^{17, 18, 72}

Boothby and Haines¹⁷⁹ discuss the value of oxygen and helium-and-oxygen mixtures before and after thyroidectomy. One can generally prevent postoperative stridor and postoperative storn and minimize the need for tracheotomy in these cases with helium-and-oxygen mixtures. Kernan and Barach¹⁴⁶ report their effectiveness in cases of obstructive lesions in the trachea and larynx. It appears almost axiomatic to employ helium-and-oxygen mixtures preoperatively and postoperatively in all difficult thyroidectomy cases. Mayo¹⁸⁰ cautions one, however, to remember that helium may mask the stridor caused by an injury to a recurrent laryngeal nerve, and thus prevent the removal of a constricting suture or hemostat.

The value of helium-and-oxygen mixtures in the treatment of asphyxia neonatorum was observed in a paper by Kane,⁵⁶ previously referred to. This observation confirms Barach's earlier expressed opinion concerning their superiority over the conventional carbon dioxide-and-oxygen mixtures. Benedict, White and Lee¹⁸¹ have successfully added helium-and-oxygen mixtures to an infant incubator to combat respiratory failure.

Pulmonary Tuberculosis

Sporadic reports have appeared in the foreign literature suggesting the use of helium in artificial pneumothorax for pulmonary tuberculosis (Reinders¹⁸² and Schedtler¹⁸³). Risen¹⁸⁴ recently made a preliminary report on the advantage of helium as a substitute for air in artificial pneumoperitoneum in the treatment of pulmonary tuberculosis. In a series of cases of pulmonary tuberculosis, periodic injections of 1000 cc. of helium into the peritoneal cavity required considerably greater time for complete appearance than did an equal quantity of

essary. Clough¹⁹⁰ described the use of helium-and-oxygen mixtures in the giving of cyclopropane general anesthesia. Employing a 50 per cent helium, 30 per cent oxygen and 20 per cent cyclopropane mixture, he observed deeper anesthesia and relief of laryngeal stridor. Thomas and Jones¹⁹¹ in an important recent paper discussed the prevention of cyclopropane-and-oxygen explosions by the use of helium. They observed that helium could be used to the best advantage in cyclopropane-and-oxygen mixtures for the prevention of explosions and to a slight advantage in ethylene or ether-and-oxygen mixtures. Bonham¹⁸⁸ stated that helium is a valuable adjunct and diluent for cyclopropane in anesthetic allergy, claiming that all true allergic cases are benefited by the administration of helium. Behnke¹⁹² summarized his extensive experience with the use of helium mixtures in his physiologic considerations of inhalation anesthesia and helium. In anesthesia it is generally considered of value in respiratory obstruction to economize physical effort, to make respiration more effective, to prevent atelectasis, as an aid in partial respiratory failure and to forestall respiratory decompression.

Encephalography

Cleveland and End¹⁹³ summarized their experiences in 41 cases studied in an effort to reduce to a minimum the untoward symptoms after encephalography. They obtained excellent results by replacing the cerebrospinal fluid with helium gas and by following this procedure with inhalation of pure oxygen until all the symptoms subsided. This method produced symptoms lasting less than half as long as those produced by oxygen encephalography and oxygen inhalation and one fifteenth as long as those produced by air encephalography.

Deep-Sea Diving and High-Pressure Work

During the last five years a tremendous literature has developed in the physiology and therapeutics of increased atmospheric pressures. The groundwork for the use of helium-and-oxygen mixtures in the field of deep-sea diving and work under greatly increased air pressure has been laid largely by the United States Public Health Service and investigators of the United States Navy. An excellent historical summary of this series of observations may be found in a recent paper by Shilling.¹⁹⁴ The studies that follow have made it possible for divers to work at greater depths for longer periods of time, have shortened the period of decompression, and have eliminated the toxic symptoms of nitrogen narcosis.

In 1925, Sayers, Yant and Hilderbrand¹⁹⁵ reported their pioneering work in the use of helium-and-oxygen mixtures to ameliorate caisson disease. They wrote:

The substitution of helium for the nitrogen ordinarily present in the air we breathe has been found to result in an atmosphere which is as respirable as that provided by nature. The results obtained indicate that helium not

only has the advantage of being less soluble than nitrogen, but also of diffusing more rapidly in the body fluids and tissues, which results in rapid elimination of the gas from the tissues during decompression. Along with mitigating the hazard of caisson illness helium should markedly increase the scope of other kinds of engineering work in compressed air.

They also demonstrated its value in allowing the decompression time to be shortened from one fourth to one eighth of the time ordinarily recommended for air. Sayers and Yant¹⁹⁶ reported further on the use of helium-and-oxygen mixtures in deep-sea diving and caisson operations.

In 1933, Stewart¹⁹⁷ summarized the status of helium at that time, saying that "divers and caisson workers can work for more extended periods and under higher pressure with greatly increased safety and comfort, and may be returned to normal pressure conditions in a fraction of the time required when compressed air is the atmosphere breathed while at work." He attributed this to the extreme insolubility of helium. Hawkins and Shilling^{198, 199} confirmed this relative insolubility in their studies of the solubility of nitrogen and of helium in blood at atmospheric and increased pressures.

End²⁰⁰ showed that if helium-and-oxygen mixtures are breathed under a pressure of 3 atmospheres, the subsequent decompression period need be only one third as long as that when nitrogen-and-oxygen mixtures are respired. He also pointed out one of the most important observations of the value of helium in diving: namely, the lessening, and in some cases the elimination, of the untoward mental and neuromuscular symptoms observed under increased air pressure. He stated that "in addition to shortening the time necessary for safe decompression, helium may also free divers from the untoward psychological effects of air at high pressure." In 1938, he²⁰¹ confirmed these impressions in reporting a world's-record dive of 420 feet in a flexible diving suit while breathing a helium-and-oxygen mixture.

The narcotic effect of greatly increased air pressures has limited the depth that divers can obtain. The limiting depth when air is breathed is generally placed at 300 to 350 feet. The toxic symptoms, ranging from dizziness to loss of consciousness, experienced by all men working in high-pressure air have been described by Behnke and his associates,^{190, 202} Shilling and Willgrube²⁰³ and others. Behnke and Yarbrough,¹⁹⁴ discussing physiologic studies of helium, state that helium-and-oxygen mixtures minimize or abolish the stupefaction and impaired motor control associated with air respiration under pressure. They²⁰⁴ found these effects greatest under argon and least under helium. A report on similar work done at the Experimental Diving Unit in Washington, D. C., may be found in a paper by Momsen.²⁰⁵ Diving tests in depths up to 500 feet were carried out under his supervision. In 1939, a story by Ellsberg²⁰⁶ concerning

helium or diving gas and attesting to its absolute necessity in diving operations appeared in a popular magazine. Additional observations in 300 cases of caisson disease observed at the Queens-Midtown Tunnel project in 1938 and statements on the value of helium-and-oxygen mixtures for rapid and safe decompression can be found in a paper by Thorne.²⁰⁷

Behnke and Willmon²⁰⁸ described the salvaging of the United States Submarine *Squalus*. This monumental work could not have been accomplished without the use of helium. Behnke^{209, 210} described two dives made to the sunken submarine 0-9 at a depth of 240 feet on June 22, 1941. The divers, although subjected to a pressure of 4.3 atmospheres, or approximately 210 pounds per square inch, felt well at the extreme depth while breathing a helium-and-oxygen mixture. In air atmospheres the narcotic effect of nitrogen renders a diver practically helpless at depths in excess of 300 feet. Behnke referred to this condition as nitrogen narcosis, for nitrogen at more than 5 atmospheres pressure is an anesthetic agent. He stated:

It is likely that the fat-solubility ratios rather than the molecular weights of these gases produce the narcotic effect of nitrogen and the benign influence of helium . . . Bends, for example, may be considered as originating from bubble formation in bone marrow, which contains about 90 per cent lipid matter. The lessened influence of bends following long exposures in compressed helium atmosphere is undoubtedly the result of the comparatively low solubility of helium in fat. The tendency to spinal-cord injury bringing about divers' paralysis likewise should be minimized in the helium atmosphere since spinal-cord substance may contain about 27 per cent lipid matter.

The above represents a further advance in the endeavors of the Experimental Diving Unit to increase the scope and depth of underwater activity.

Aero-otitis Media

Armstrong and Heim²¹¹ suggest the term "aero-otitis media" to describe the syndrome of inflammation, discomfort, pain, tinnitus and deafness observed in aircraft pilots during changes of altitude. They attribute this to lack of ventilation of the middle ear owing to failure or inability to open the eustachian tube voluntarily when necessary. Lovelace, Mayo and Boothby²¹² describe the prevention and alleviation of this troublesome syndrome in aviators and passengers by breathing helium-and-oxygen mixtures. They attribute the value of this mixture to the high rate of diffusibility of helium as compared with that by nitrogen. Helium probably diffuses through the sinus ostia or through the eustachian tube more rapidly than does nitrogen. Thus the equalization of pressure between the middle ear and the external barometric pressure occurs more readily. A similar report was made by Lovelace¹ and Henrich.²¹³

Hall²¹⁴ was unable to confirm the above observations of Lovelace et al. He presented experimental evidence that respiration of helium-and-oxygen mixtures during descents at various rates does not sig-

nificantly alleviate the painful ear symptoms resulting from rapid changes in barometric pressure. He demonstrated, however, that slightly greater changes of barometric pressure are necessary to produce the various degrees of otalgia in subjects who descend while breathing helium-and-oxygen mixtures than are necessary in those who descend while breathing atmospheric air. He did not consider the administration of helium-and-oxygen mixtures practical for the prevention of painful ear symptoms.

Chester and Drooker²¹⁵ made a careful investigation of the physiologic changes in the ear during flight. They approached the therapy of aero-otitis media and aerosinusitis by attempting to restore the normal functions of the eustachian tubes and sinuses, thus correcting the pressure gradients. They found most effective cocaine, Neo-Synephrin, the eustachian catheter and politzerization. A similar report is that of Wiseheart,²¹⁶ who employed instillation and suction procedures.

Tubal or Sinus Block

A similar syndrome may be observed when one is going from atmospheric pressure to increased air pressure. Divers generally complain of blocked ears and inability to clear the ears or to equalize pressure. Crosson, Jones and Sayers²¹⁷ observed so-called "tubal or sinus block" among compressed-air workers in tunnel operations in New York City. Employing a small, portable, 80 per cent helium and 20 per cent oxygen, breathing outfit, they obtained immediate relief in 82 of 84 workers. These men were able to re-enter the tunnel and resume their work with no delay or discomfort. Similar observations in compressed-air workers were made by Requarth²¹⁸ and Thorne.²¹⁹ Thorne found helium-and-oxygen inhalations more efficacious than nasal-drop therapy in the management of 306 cases of ear block. He stressed the importance of instituting inhalation therapy as quickly as possible after the onset of symptoms of ear block, for once the firm adhesions of the walls of the eustachian tubes have formed secondary to the existing infection, inhalation treatment is unsuccessful.

Physics of Helium Mixtures

An interesting series of papers concerned with the practical physics of mixtures of oxygen, helium and nitrogen has appeared from the Mayo Clinic. Dublin et al.^{220, 221} made analyses of the percentages of oxygen, helium and nitrogen mixtures by determining the velocity of sound in these mixtures and described an apparatus for doing so.

The voice changes caused by effective helium-and-oxygen administration may be amusing or frightening to the uninitiated. The effect on men can best be described by the term "effeminate." A deep baritone voice develops a lyric-tenor quality, and a man with a tenor voice can only squeak.¹⁹⁰ This

has been explained as due to the fact that the muscles of the larynx are unconsciously set to cause a certain sound in air, and that when breathing a medium so much lighter the sound produced is much changed from normal.²²² Behnke¹⁹² observed that this peculiar nasal quality to the voice does not disappear at increased barometric pressures. The density of the helium-and-oxygen mixture in a pressure chamber can be increased to that of air at atmospheric pressure and the voice still remains abnormal. This renders difficult the problem of communicating with the deep-sea diver by telephone. Divers experienced in breathing helium-and-oxygen mixtures can, however, modify these voice changes to approach the normal.

Dublin, Baldes and Williams²²³ made oscillographic studies on these voice changes. They determined that the alterations consist of a variation in overtones. The frequency of the fundamental vibrations remains the same. The low density of the helium-and-oxygen mixture impedes the vibration of the vocal cords less than does air. This may result in a change in the original production of overtones. Also, because of the lower density, the velocity of sound with helium-and-oxygen mixtures is increased. This probably causes the vocal resonators to amplify different overtones. Which of these differences is more important was not determined.

Behnke and Yarbrough¹⁹⁴ made a splendid contribution from the Experimental Diving Unit of the United States Navy in their paper on the physiologic studies of helium. Their detailed study offered the following conclusions. First, the most striking effect of helium is a feeling of normality, in contrast with the usual intoxication and sense of pressure and depth associated with high pressures. This improved mental condition of the diver is more important than the advantage of shortening the decompression time. Second, the helium content of the body should be about 45 per cent as high as the nitrogen content when the same tension of each gas is breathed. The decreased solubility of helium in fat compared with that of nitrogen theoretically decreases the elimination time of this gas from the body and lessens the possibility of spinal-cord injury. Third, the comparative low fat-and-water solubility ratio of helium compared with that of nitrogen explains the lack of anesthetic effect in helium breathing under pressure as compared with nitrogen breathing under pressure. The latter condition was previously referred to as nitrogen narcosis. Fourth, the helium content of the body is about 40 per cent of the nitrogen content for corresponding gas tensions. At atmospheric pressure 99 per cent of the helium content is eliminated in five and a half hours, or in about half the time required for nitrogen desaturation. Lastly, by periodic determinations of the inert-gas content of the urine a quantitative estimate of gas elimination can be obtained and the occurrence of bends can frequently be prognosticated.

Behnke¹⁹² in discussing the temperature effects produced by helium states that twice as much electrical heat must be supplied to keep a diver warm when he is surrounded by a helium-and-oxygen mixture compared with an air atmosphere. Hardy²²⁴ suggests that the increased molecular motion of helium atoms compared with that of nitrogen results in a greater heat loss from the body through conduction.

Dean and Visscher²²⁵ and Visscher,²²⁶ searching for the physical basis for the therapeutic use of helium, made a study of the kinetics of lung ventilation in dogs. They state that when air movement is turbulent, helium-and-oxygen mixtures move more easily than does air. They found no appreciable difference in the work required to move air or helium-and-oxygen mixtures in animals and in human beings with normal airways and normal lungs. The most significant effect of helium was in reducing the work of moving the gas across an obstruction in the large airways. In going from air to helium-and-oxygen mixtures they demonstrated in laboratory animals with tracheal obstruction a 40 per cent reduction in the work of ventilation. They concluded that helium is useful in obstruction of the upper airways — laryngeal, tracheal or bronchial. These observations were in entire agreement with those previously reported by Barach. They further stated:

Where there is a localized obstruction so that air passes at high velocity through a short, narrow stretch and then can expand into a wider passage where its velocity can be less, under these circumstances turbulence is set up, and therefore substitution of helium for nitrogen in oxygen mixtures is most advantageous in reducing the work of breathing. The mechanism is by increasing the velocity at which there can be streamline flow.

Dean and Visscher conclude further that helium breathing has not been conspicuously successful in uncomplicated asthma, presumably because the obstruction to air flow is in the small respiratory pathways, the bronchioles, and there even nitrogen and oxygen move in streamline flow. The long series previously referred to attesting to its value in bronchial asthma does not bear out the above statement. Furthermore, they state that Barach ignored the factor of viscosity in his earlier explanation of the physiologic basis of inhaling helium-and-oxygen mixtures. In 1935, Barach¹⁶⁶⁻¹⁶⁸ stated in a general discussion at the meeting of the American Society for Clinical Investigation:

A physical basis for the use of helium is as follows: According to Graham's law the rate of diffusion of a gas is inversely proportional to the square root of its density. This law applies also to effusion, that is, the passage of a gas through small orifices, which is especially applicable to the problem here discussed. Since the viscosity of helium is slightly greater than that of nitrogen, there is no reduction in frictional resistance, and Poiseuille's law does not become involved in an explanation of the results. The point involved is that the obstruction exists for a space so limited in extent as to obey the law of diffusion or effusion rather than Poiseuille's law. Under these circumstances the pressure required for moving a mixture of helium and oxygen would be approximately one half that for moving air. . . . In severe dyspnea the

DIFFERENTIAL DIAGNOSIS

DR. ARTHUR HERTIG*: It seems to me from the history that the differential diagnosis involves some form of pregnancy or some complication of the latter in spite of the fact that the patient was fifty-two years old. Of course it is known that pregnancy can occur in a patient over fifty years of age. In keeping with the diagnosis of pregnancy or of some of its sequelae are the following facts. The patient had perfectly regular periods until she missed two, eight months prior to entry. She then had what she thought was a menstrual period, which, if you look at the record, shows that it was somewhat atypical and could have been anovulatory bleeding from a nonmenstrual endometrium. The character of the bleeding, however, was in keeping with some sort of threatened abortion — intermittent bleeding, sometimes red, and then steadying down to a brownish stain. When this occurs in a younger woman, we believe that it is pathognomonic of threatened or incomplete abortion due to some sort of blighted ovum.

The question comes up whether she had some sort of complication from the preceding pregnancy. Her last pregnancy was twelve years before admission, and some complication is perfectly within the realm of possibility. There are cases recorded in which a chorionepithelioma lay dormant for a great many years and then flared up. I do not believe that this patient had a chorionepithelioma. She had a relatively symmetrical uterus that was enlarged to a size compatible with a four months' pregnancy. It is inconceivable from my personal experience or from anything I have read to have a uterus enlarge symmetrically to that size and be associated with chorionepithelioma.

She could have had a hydatidiform mole which, not only clinically but pathologically, can be defined as a type of temporarily missed abortion. She had a uterus inconsistent with her dates. If she was pregnant at all, she had a four months' uterus, instead of an eight months' one, and such a discrepancy ordinarily rules out hydatidiform mole. Most of us have taught students that all molar uteri are bigger than they should be according to the estimated date of confinement. Actually they may be the same size, smaller or larger.

My diagnosis in this case is a missed abortion of eight months' duration within a uterus that was compatible with a four months' pregnancy. It probably had in it an ovum that was blighted or a dead embryo, the placental tissue of which was living; otherwise a qualitatively positive Aschheim-Zondek test would not have been obtained. It is quite possible, on the basis of our experience at the Boston Lying-in Hospital and the Free Hospital for Women, that she had a placenta accreta as the basis of her missed abortion.

*Pathologist, Boston Lying-in Hospital, and Free Hospital for Women, Brookline.

On the purely gynecologic side, it is possible that she had a single large fibroid, which may grossly simulate a pregnant uterus. Since, however, there is no reason why such a patient would have a qualitatively positive Aschheim-Zondek test, I am forced to conclude that she had a missed abortion, probably associated with a dead fetus, which might not have been visible by x-ray; she may have had a placenta accreta, but probably not. At any rate, she had an enlarged uterus and was in the age group in which, even though she did have a missed abortion, she should have had a hysterectomy, because a missed abortion interrupted from below in elderly patients is not without its hazards.

DR. FRANCIS M. INGERSOLL: I saw this patient in the Out Patient Department, and having just come back from a service at the Lying-in Hospital, I thought that she was pregnant. Since she was bleeding, a pelvic examination was not performed. She had a positive Aschheim-Zondek test, and Dr. Albright's laboratory did the subsequent quantitative Friedman tests. We believed, just as Dr. Hertig did, that it was something related to pregnancy and that the best way to treat the patient, in view of her age, was by hysterectomy, which was performed. Dr. Donald N. Sweeny did the operation. The uterus was symmetrically enlarged, and the broad ligaments were full of varices, but the operation was completed without difficulty.

DR. JOHN L. NEWELL: The fact that on pelvic examination the cervix admitted one finger makes me believe that the patient must have had some labor. With a missed abortion at this stage one ought to be able to feel fetal bones by direct palpation, even if they had become necrotic. By x-ray, however, they would be difficult to see because of gas.

DR. LAURENCE L. ROBBINS: I cannot see anything in the x-ray films that suggests ossification, but as Dr. Newell said, there is sufficient material in the bowel so that it could be missed.

DR. HERTIG: It would not surprise me if the patient had a mole. The story is perfectly consistent with such a diagnosis.

CLINICAL DIAGNOSIS

Chorionepithelioma?

Pregnancy?

Hydatidiform mole?

DR. HERTIG'S DIAGNOSIS

Missed abortion, probably associated with a dead fetus and possibly with a placenta accreta or a hydatidiform mole.

ANATOMICAL DIAGNOSIS

Hydatidiform mole.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The uterus that we received was a large one and was filled with the

grapelike clusters characteristic of a hydatidiform mole. At the time of operation they could be seen extruding from the external os.

DR. JOE V. MEIGS: Are you not surprised, Dr. Hertig, that the titer of the Friedman test was not higher?

DR. HERTIG: It is extremely variable in moles, ranging all the way from total absence of chorionic gonadotropic hormone to 1,000,000 units per liter—a very high titer. The more I see of moles, the less I am surprised about anything that they may do.

DR. CASTLEMAN: There was a fair amount of trophoblastic tissue in the uterus, but no evidence of chorionepithelioma.

DR. HERTIG: I meant to bring out the point that the fact the patient thought she felt a fetus does not mean anything. I remember one case of a mole at the Boston Lying-in Hospital in which the patient, who had had eight or ten children and who therefore knew what fetal movements felt like, was sure she felt fetal movements the day before we operated for a mole.

CASE 30162

PRESENTATION OF CASE

A fifty-one-year-old housewife was admitted to the hospital because of irregular vaginal bleeding.

The patient first menstruated at the age of fourteen. The periods were regular at twenty-eight-day intervals. They lasted five or six days, requiring towels rather than pads. She had considerable discomfort and was forced to remain in bed during the periods. About four months before admission, after having had no menstrual bleeding for six weeks, she began to bleed and continued for seven weeks. She was given ergotrate and "injections" (the nature of which was not known) without relief. There was no tenderness in the right groin. Five days prior to entry she again began to bleed profusely. This persisted. There was no anorexia, weight loss, chills, fever or night sweats.

She had had two full-term normal deliveries at twenty-five and twenty-eight years of age.

Physical examination showed a well-developed, well-nourished, pale woman in no distress. The lungs were clear. There was some tenderness, as well as a suggestive mass, in the lower abdomen. Pelvic examination showed a lacerated perineum, a large, lacerated cervix, which was slightly hard to palpation, and an irregularly enlarged uterus.

The blood pressure was 140 systolic, 80 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a hemoglobin of 6.6 gm. per 100 cc. The urine was normal. A blood Hinton test was negative.

She was given a transfusion of 500 cc. of fresh whole blood.

An operation was performed on the second hospital day.

DIFFERENTIAL DIAGNOSIS

DR. FRANCIS M. INGERSOLL: This case, it seems to me, resolves itself into that of a fifty-one-year-old woman, para II, whose periods have been regular until four months prior to operation, at which time she had a period of amenorrhea for six weeks and then bled excessively, eventually reaching a hemoglobin level of 6.6 gm. Physical examination was negative except for an irregularly enlarged uterus. The average surgeon would have a bit of an advantage because he would do a dilatation and curettage before making a diagnosis. Unfortunately, I cannot do a dilatation and curettage or a pelvic examination under ether to help me establish a diagnosis.

Of course, any patient at fifty-one is either in the menopause or approaching it. At the menopause the ovarian function ceases. This patient may not have been ovulating and may have had anovulatory bleeding, which, however, does not usually result in a hemoglobin level as low as 6.6 gm. I think that we have to postulate a disease besides menopause.

The six weeks of amenorrhea followed by bleeding suggest pregnancy. Pregnancy is infrequent at fifty-one, but we all know that it occurs. If the patient were a younger woman with six weeks of amenorrhea and then hemorrhage, one would think that some complication of pregnancy was likely. She could have had a blighted ovum on the basis of fibroid uterus, which would account for the size of the uterus and possibly for the rest of the picture. That, however, is unlikely, as is a hydatid mole. Chorionepithelioma is a rare disease, and I think that we can disregard it.

A tumor of the uterus might have accounted for the irregularly enlarged uterus and the bleeding, and the first one to be thought of is a fibroid. Fibroids are frequent in postmenopausal women, about one out of every five women at autopsy having fibroid tumors in the uterus. Fibroid tumors in this age group can also cause abnormal massive bleeding, such as this woman had. The mechanism of bleeding in fibroid tumors is not known, but the increase in the menstrual surface may account for the bleeding. It does not seem to me, however, that a fibroid alone could account for this picture. Possibly it was a fibroid, and was one of the 1 per cent that become sarcomatous. If she had a sarcoma of the uterus, one would expect a marked weight loss or other evidence of systemic disturbance that would point toward that type of malignancy.

It is fairly well known that carcinoma of the endometrium is frequently associated with a fibroid tumor. Scheffey,¹ in a paper read before the Boston Obstetrical Society on October 16, 1943, reported

via the uterine vein or plexus of veins going into the broad ligament. One must regard this process as a low-grade malignancy because there was extension outside the uterus. This case is similar to those reported by Frank² in 1932. He called this disease, "fibromyosis"—an unclassified plexiform endolymphatic proliferation of the uterus. In his series

had extended into the broad ligaments. He called it a benign leiomyosarcoma that had invaded the lymphatics.

I recently attended a meeting of the New York Obstetrical Society where Dr. J. Raglan Miller, of Hartford, discussed this condition under the name "stromal endometriosis." He reported 4 cases and considered them benign. At a meeting at Hot Springs, Virginia, Dr. James R. Goodall, of Montreal, told me of his monograph on stromal endometriosis.⁴ The tumors he described involved the stroma, but not the glandular structure. Dr. Goodall thought that if the ovary was removed this tumor would stop growing. At the New York meeting Dr. Frank stated that the tumor was of low-grade malignancy and that he did not believe that it was a stromal endometriosis.

Differential stains show that the supporting reticulum of this type of tumor is not similar to that of fibroids.

DR. CASTLEMAN: It is interesting that this patient also had endometriosis on the surface of the uterus.

DR. HERTIG: I must say that in this case the term "stromal endometriosis" does not seem logical: first, because of the age of the patient and, second, because of the lack of bleeding into the tumor itself.

DR. MEIGS: The patient had no glandular tissue.

DR. HERTIG: It is not the glands that bleed; it is the stroma.

DR. CASTLEMAN: The intravascular growths were purplish red, indicating that there was bleeding into the tumor.



FIGURE 2. Cross Section of Myometrium Showing Intrastromal Fibromyomatous Plugs.

of 3 cases, 1 patient finally died of metastases and 2 were cured by resection, although 1 had a recurrence. It is not really a leiomyosarcoma because sections do not show true muscle cells; the tumor apparently arises from the endometrial stroma.

DR. MEIGS: In my book,³ a picture of one of these is titled "sarcoma of the uterus"; this, incidentally, is the case that Dr. Hartwell showed you. The lesion

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standing, to retire under the provisions of Chapter I, Section 5, of the by-laws, such retirement to be effective as of January 1, 1944:

Ayer, T. H. (Worcester). 9 High Street, Westboro.
 Cogan, Joseph A. (Suffolk). 419 Boylston Street, Boston.
 Ellis, Frederick W. (Middlesex South). 1175 Centre Street, Newton.
 Hunt, George P. (Berkshire). 131 East Housatonic Street, Pittsfield.
 Lazarus, Benjamin (Middlesex South). 61 Halcyon Road, Newton Centre.
 Levins, N. N. (Suffolk). 30 Chambers Street, Boston.
 Lynch, Charles F. (Hampden). 1387 Main Street, Springfield.
 Mackay, Edward H. (Worcester). 42 Walnut Street, Clinton.
 McPherson, George E. (Hampshire). Amherst.
 Slaughter, Emma E. Y. (Middlesex North). 545 School Street, Lowell.
 Smith, William H. (Suffolk). 8 Marlboro Street, Boston.
 Wells, Charles E. (Norfolk South). 15 Union Street, Randolph.

Allowed the following named fellow, applying for retirement, to retire with remission of dues owed the Society under the provisions of Chapter I, Section 5, of the by-laws, such retirement to be effective as of January 1, 1944:

Ledbury, J. William (Worcester). 100 North Main Street, Uxbridge.

Accepted the resignations of the following named fellows, under the provisions of Chapter I, Section 7, of the by-laws, such resignations to be effective as of January 1, 1944:

Ashmore, Buell L. (nonresident). Veterans Administration Facility, Excelsior Springs, Missouri.
 Coffin, Betsy (nonresident). Piedmont College, Demorest, Georgia.
 Odeneal, Thomas H. (Essex South). 79½ Prospect Street, Gloucester.
 Young, David A. (nonresident). 715 Boston Building, Salt Lake City, Utah.
 Ziegler, Edwin E. (nonresident). St. Luke's Hospital, Bethlehem, Pa.

Allowed the following named fellow to change his membership from one district society to another, without change of legal residence, under the provisions of Chapter III, Section 3, of the by-laws:

Emmons, Henry M., 354 Commonwealth Avenue, Boston (Suffolk to Norfolk).

Remitted the dues for 1944 of the following named fellows, both of whom are ill and incapacitated, under the provisions of Chapter I, Section 6, of the by-laws:

Krieger, William L. (Norfolk South). 15 Lincoln Avenue, Wollaston.
 Sawyer, Alpha R. (Norfolk). 171 Walnut Hill Road, Chestnut Hill.

Reinstated the following named physicians, under the provisions of Chapter I, Section 10, of the by-laws, who had been deprived of fellowship for the nonpayment of dues, provided their arrears in dues at the time they were dropped plus the dues for 1944 be paid to the treasurer of the Society:

Kudish, Benedict (Suffolk). U. S. Quarantine Station, 50 Central Wharf, Boston. Joined 1934. Deprived 1941.

Prenn, Joseph (Suffolk). 15 Bay State Road, Boston. Joined 1908. Deprived 1939.
 Savage, Ross E. (Essex South). Masonic Building, Gloucester. Joined 1918. Deprived 1935.
 Udelson, Barnet A. (Norfolk). 460 Geneva Avenue, Dorchester. Joined 1934. Deprived 1941.

The personnel of the Committee on Membership is as follows: Harlan F. Newton, *chairman*; John E. Fish; Peirce H. Leavitt; Sumner H. Remick; and Samuel N. Vose. The representatives of the supervising censors are as follows: William H. Allen; H. Quimby Gallupe; and Albert E. Parkhurst.

MICHAEL A. TIGHE, M.D., *Secretary*
 Executive Committee

DEATHS

HATCH — Ralph A. Hatch, M.D., of Brookline, died April 1. He was in his sixty-third year.

Dr. Hatch received his degree from Harvard Medical School in 1906, and had limited his practice to ophthalmology. He was a member of the Massachusetts Medical Society, the American Medical Association and the New England Ophthalmological Society.

His widow and two sons survive.

LASERTE — Charles J. Laserte, M.D., of Leominster, died April 14. He was in his sixty-third year.

Dr. Laserte received his degree from Baltimore Medical College in 1905. He was a member of the Massachusetts Medical Society and the American Medical Association.

YUDIN — Hyman Yudin, M.D., of Beverly, died recently. He was in his fifty-fourth year.

Dr. Yudin received his degree from the College of Physicians and Surgeons, Boston, in 1918. He was a member of the Massachusetts Medical Society and the American Medical Association.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

CLINIC	DATE	CLINIC CONSULTANT
Salem	May 1	Paul W. Hugenberger
Haverhill	May 3	William T. Green
Lowell	May 5	Albert H. Brewster
Springfield	May 10	Garry deN. Hough, Jr.
Brockton	May 11	George W. Van Gorder
Pittsfield	May 15	Frank A. Slowick
Worcester	May 19	John W. O'Meara
Fall River	May 22	Eugene A. McCarthy
Hyannis	May 23	Paul L. Norton

NOTICES

BOSTON GASTROENTEROLOGICAL SOCIETY

The next meeting of the Boston Gastroenterological Society will be held in the auditorium of the Carney Hospital on Thursday, April 27, at 12 m. The following subjects will be discussed:

Unusual Complications in the Gastrointestinal Tract following Surgery. Dr. William E. Browne.
 Polyps of the Bowel. Dr. Timothy F. P. Lyons.
 Management of Massive Duodenal Hemorrhage. Dr. Francis J. West.

(Continued on page 2)

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ANDROGEN CONTROL IN CARCINOMA OF THE PROSTATE*

JOHN P. BOWLER, M.D.,† AND SCOTT F. PEDLEY, M.D.‡

HANOVER, NEW HAMPSHIRE

THIS paper presents a brief report of the early results of castration in 22 cases of carcinoma of the prostate seen during 1942. The physiologic rationale of castration has perhaps been the outstanding item in recent urologic literature, much of which has been controversial and contradictory. With the understanding that many details of the present concept are missing, some not proved and others doubtless later to be changed or disproved, the present basis of attack will be briefly outlined.

Dr. Charles Mayo has been quoted as having made the statement many years ago, "No matter what you do for carcinoma of the prostate, you do the wrong thing." The persistence of this pessimistic attitude has not been without a basis in the poor results generally achieved. Until recently, transurethral resection for the relief of obstruction and radiation for the relief of pain have contributed considerable alleviation, temporary, to be sure, to these patients. The position of the advocates of radical perineal prostatectomy as the only possible direct attack on carcinoma of the prostate is surgically sound, but it fails to meet the general problem, for many reasons. First, the disease originates most frequently in the posterior lamella, thereby giving rise to urinary symptoms relatively late in its development; second, the carcinoma is slow growing and is well advanced by the time that the typical patient of prostatic age, expecting as he does a certain degree of urinary difficulty, decides to obtain medical advice. The most enthusiastic supporters of radical perineal prostatectomy agree that the percentage of cases to which it can be applied — namely, those in which a malignant lesion is still confined within the prostate capsule when the patient is first seen — is not over 5 per cent. At least 95 per cent of prostatic carcinomas must therefore be treated by other methods. The importance of the lesion is

brought out by the fact that the number of men living into the prostatic age — that beyond sixty-five — doubled in the United States between 1911 and 1935.¹

Beginning in 1933, Dmochowski,² Kutscher and Wolbergs,³ the Gutmans⁴ and other workers investigating the sources of acid phosphatase in urine discovered that normal human prostate tissue is extremely rich in this material. Acid phosphatase is an enzyme, a constituent of many tissues of the body, but, as noted by these writers and others, it is present in far greater concentration in the adult prostate gland and prostatic fluid than in any other part of the body. Significant is the fact that it occurs in extremely low concentrations in the prepubescent prostate. Most carcinomatous prostate tissue contains large amounts of acid phosphatase, whereas highly malignant tumors, being made up of functionally immature cells, contain but little of it. When metastasis of a prostatic carcinoma occurs, presumably the acid phosphatase is allowed to escape into the blood and lymph and the blood-serum level is elevated. The acid phosphatase is measured in units per 100 cc. of serum, 3 to 5 units being regarded as the range of normal by various workers. Elevated levels may fail to appear because of insufficient invasion, lack of differentiation of the tumor or preceding treatments, as will be discussed later.

Serum alkaline phosphatase is likewise an enzyme, but is less specific than acid phosphatase regarding its prostatic origin. It is elaborated at sites of osteoblastic activity, particularly bony metastases where new bone is being formed. Therefore, Paget's disease and other lesions characterized by osteosclerosis must be excluded if one employs the level of this substance as a measure of osteoblastic metastatic lesions.

It can be inferred, then, that elevation of serum acid phosphatase signifies prostatic-cell activity communicable to the blood stream, therefore of extracapsular prostatic tissue and therefore presumably of carcinoma. Likewise, elevation of the

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†Presented at the annual meeting of the New Hampshire Medical Society, Manchester, May 11, 1943.

‡Dean, Dartmouth Medical School, surgeon, Mary Hitchcock Memorial Hospital.

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serum alkaline phosphatase accompanies the change in the metastatic bone lesion from one of osteolytic to one of osteoblastic type, thus indicating sclerosis and regression as a result of a defensive reaction of bone to the tumor.

The findings of Sullivan⁵ and the Gutmans⁶ (Table 1) illustrate clearly the incidence of elevated values in carcinoma of the prostate in the presence of metas-

TABLE 1. *Acid Serum Phosphatase Levels in Various Prostatic Conditions (adapted from Sullivan⁵ and Gutman and Gutman⁶).*

CONDITION	No OF CASES	PERCENTAGES OF CASES WITH VARIOUS LEVELS (UNITS) OF ACID SERUM PHOSPHATASE					
		30 OR LESS	30-49	50-99	100-999	1000 OR OVER	
Prostatic carcinoma							
Bone metastases (x-ray)	130	15	12	25	35	9	4
No bone metastases (x-ray)	70	89	11				
Prostatic hypertrophy	75	100					
Prostatitis	10	100					
Nonprostatic disease	570	90	8	2			
Normal	30	100					

tases. In a series of 200 cases of prostatic carcinoma, 85 per cent of 130 cases with demonstrable bone metastases showed an elevated acid serum phosphatase. Seventy cases without metastases as shown by x-ray examination showed slight elevation in 11 per cent. Glands with benign hypertrophy or prostatitis and normal glands showed no elevation, whereas of 570 cases of nonprostatic disease ten per cent showed elevation, demonstrating extraprostatic origin of acid phosphatase. It is thus evident that the serum acid phosphatase is not elevated in cases of prostatic carcinoma confined to the capsule of the gland. Unfortunately, therefore, such elevation is not corroborative evidence of the nature of the lesion prior to metastatic or extracapsular involvement.

The first investigators to recognize the implications of the results of this experimental research were Huggins and his associates,⁷⁻⁹ who at that time had gone back, so to speak, to investigate the effect of castration or administration of estrogens on prostatic hypertrophy in dogs. On the basis of this work, they published in 1941 an outline of androgen control of prostatic tissue by surgical castration. They reported several cases of metastatic prostate carcinoma subjected to castration in which there was a sharp postoperative reduction in serum acid phosphatase and a rise in serum alkaline phosphatase followed by a gradual decline, and in which these chemical changes were accompanied by marked clinical improvement.

In summary, the rationale of the present approach is the removal of stimulation of the prostate cells by androgen. This is being effected by surgical castration, irradiation castration, neutralization with administration of estrogens and combinations of these methods (Fig. 1).

As shown, surgical castration removed the source of androgen, whereas estrogen may be administered as its neutralizer. In other words, the adult pros-

tatic epithelium is activated by the androgenic gonadotropic hormone, resulting in an increase of the tumor, in an elevated serum acid phosphatase and in the production of symptoms. Castration removes the source of androgen and inactivates the prostatic epithelium, the tumor decreases, the acid phosphatase decreases, and the symptoms decrease. The effect of androgen is similarly neutralized by the use of estrogen.

The use of estrogen as the sole therapeutic program has been reported by Herbst¹⁰ and others as having favorable results, both symptomatically and regarding changes in the gland itself. We have not

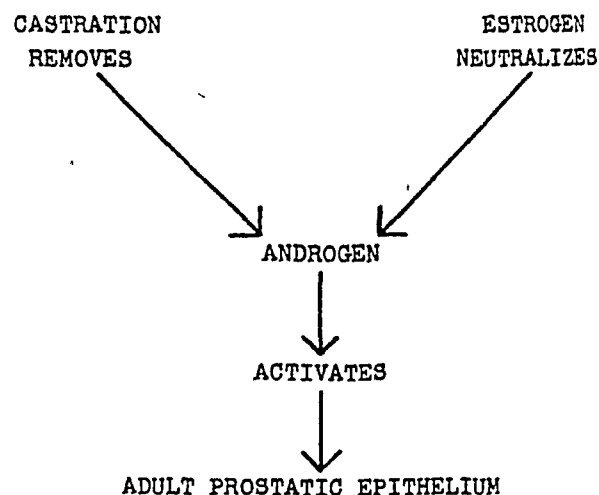


FIGURE 1. *Mode of Action of Castration and Estrogen Therapy.*

used it in any case as the sole procedure, but have reserved it for the treatment of delayed recurrences following orchidectomy, with at least temporary beneficial results in several cases.

Irradiation castration has been applied for some years by Munger,¹¹ who seems to think that the results are quite comparable with those of surgical castration. It is highly probable that irradiation castration has in the past been unwittingly accomplished by inclusion of the scrotal field in deep-therapy exposures.

In every case of the present series a surgical castration was done, at times in conjunction with radiation and administration of estrogen in cases in a hopelessly advanced stage. The usual complete castration was performed in the early cases of the series, but in the great majority a subcapsular orchidectomy was done after the manner described by Chute¹² in 1942. Figure 2 demonstrates the procedure. Through separate lineal scrotal incisions, the testicle is delivered from the scrotum. The tunica albuginea is then incised longitudinally opposite the epididymis, and the entire rete testis is removed en masse by instrumental and finger curetting. After ligation of the intracapsular blood supply of the rete, the capsule is closed with a locked suture, the tissues are restored to the scrotum, the skin incisions are

closed, and a suspensory dressing is applied. The capsule of the testis usually fills with blood, which becomes organized, and there is but little change in the palpable or visible contents of the scrotum. The latter advantage appears to be of some importance in the introspective processes of the patient. In this connection it is of interest that we have yet to encounter refusal of this procedure by any patient.

All the cases in this series were those of adenocarcinoma of the prostate gland, proved either by demonstrable metastatic bone lesions or by pathological

third group at the time of operation had received deep x-ray therapy from one to two years previously.

Bone metastasis was demonstrable by x-ray examination in 10 cases, but in only 6 of these was pain given as a symptom. Thus, 4 cases without pain showed bone involvement, whereas in 4 with pain no metastatic extension could be shown. This observation seemed to contradict an old concept that pain in the back, lumbar region or buttocks is complete corroborative evidence of extension of a physically

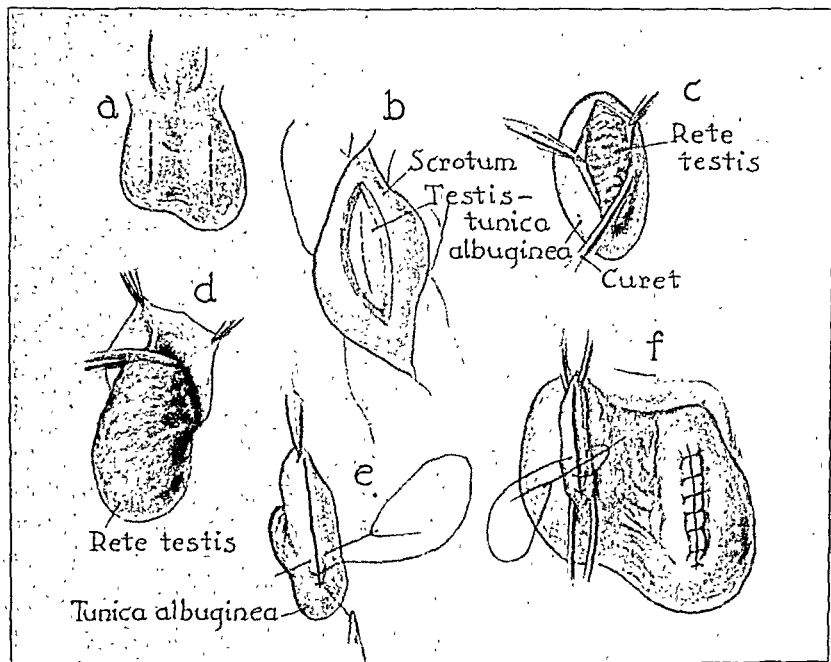


FIGURE 2. Operative Steps in Castration.

examination of removed tissue. The average age of the patients was seventy years, ranging from fifty-four to eighty-six years. Dysuria was present in 17 cases, an appreciable residual urine in 10, and complete urinary obstruction in 4. An orchidectomy was carried out as the sole procedure in 4 cases; it was done following transurethral resection in 15 cases, and at varying intervals following transurethral resection or prostatectomy elsewhere in 3 cases. The patients in the first group received no x-ray therapy, 3 of the second group received it either previously or combined with the orchidectomy because of the advanced stage of disease, and all 3 patients in the

diagnosable malignant prostate. This concept probably still holds true, but the point to which it leads is that a negative x-ray examination of the lumbar spine and pelvis, like all negative findings, does not justify exclusion of bone metastasis.

This point was forcibly demonstrated by a sixty-seven-year-old patient who had received transurethral resection and deep x-ray therapy elsewhere. The preliminary x-ray films were negative. Two and a half months following the performance of orchidectomy there was extensive osteosclerosis of the third lumbar vertebra and sharply defined areas were seen in both iliums. On review of the preoperative

films by the X-ray Department, fine variations in density could be demonstrated at the sites of these later obvious metastases.

In another case of obvious clinical carcinoma of the prostate, a preoperative bone roentgenogram was definitely negative. Rectal examination revealed characteristic induration and irregularity of the gland. The clinical response of cessation of urinary symptoms was most marked and remained so. On postoperative check-up three months following orchidectomy, roentgenograms showed obvious bone involvement in the right ilium and symphysis.

It is in such cases that the serum acid phosphatase level is of great significance. In 1 such case it was high, showing a preoperative value of 15 units, dropping to 7.8 in the following two months, with a complete stabilization of symptoms that has continued to the present time. Phosphatase determinations are, however, affected by many factors and require a lengthy and painstaking technic, and it has been found necessary to leave this work in the hands of a specially trained technician. At times there has been a disturbing lack of correlation with the clinical course, but we are inclined to attribute this lack to as yet unknown factors of physiologic or pathologic activity.

The serum acid phosphatase level was significantly elevated in 14 cases. One of the highest of these levels occurred in a sixty-four-year-old patient who when first seen was completely disabled, and who was admitted by ambulance, with extensive local and bony involvement and enlarged left supraclavicular nodes that were positive on biopsy. This was one of the most extreme cases encountered. All possible means of therapy were used. A transurethral resection was done because of marked obstruction, deep x-ray therapy was indicated, stilbestrol was given, and an orchidectomy was done. The preoperative x-ray film showed extensive osteoblastic metastases throughout the pelvis. Films taken three months after the orchidectomy showed extreme sclerosing of these areas, which was particularly obvious in the right ilium. By that time there was a 75 per cent recession in the supraclavicular nodes, and the general clinical result was dramatic. This improvement continued for seven months and the patient returned to overseeing his farm. At the end of eight months of normal health, extension and pain recurred, and a rapid progression to a general carcinomatosis followed. This late failure was in contradiction to what was to be expected from the initial clinical picture.

Recalcification of bone following orchidectomy is exemplified in a patient of seventy-seven presenting marked dysuria and bladder irritability, with extensive destruction of the left pubis. Following orchidectomy alone there was almost immediate complete relief of the bladder symptoms, and within a few months there was a dense, smooth and complete

reconstruction of the pubis, with relief of pain walking. This improvement has now continued one year. The patient was one of the 4 on whom orchidectomy only was done, and it is of interest that the results in this small group, as yet unexplained, are uniformly excellent to date.

Response to orchidectomy following relapse after x-ray therapy is illustrated by a fifty-four-year-old patient who was first seen in November, 1941, with obstruction and bony metastasis. Following resection and an intensive course of deep x-ray therapy which included x-ray castration, he was relieved three months. When seen in June, 1942, he was completely disabled. Following orchidectomy he was relieved of all pain and performed general farm work all that summer and fall. Sixteen months after the cessation of the original treatment and months after the orchidectomy, he returned with recurrence and progression, which could not be controlled.

Contrasted with the above case is a seventy-year-old patient who had a similar management before orchidectomy. In March, 1941, he had had a transurethral resection and deep x-ray treatment elsewhere. His complaint when seen by us was recurrent pain, particularly in both thighs, and inability to flex or adduct the right thigh. X-ray films taken two months following orchidectomy showed marked sclerosis of bone. There followed complete relief from all pain and muscular disability, and the patient was able to return to the care of his farm.

We are interested in grading these tumors in relation with the phosphatase activity and clinical variations, but as yet our series is not large enough to permit valid conclusions.

Obviously, more time is required to corroborate our present observations, but the promptness and completeness of symptomatic relief as compared with past methods has been impressive. As yet no other means of therapy for far-advanced cases offers relief for so long or so completely as do the procedures described above. The relief and comfort afforded in cases of remission following routine deep x-ray therapy have been striking. Many carcinomas of the prostate are of low grade and many patients with such tumors live for long periods, and it is much too early to judge the long-time effectiveness of the procedures. On the other hand, these cases present the first tumors available to the clinician in large numbers in which the question arises whether cancer is the result merely of an intrinsic urge of a cell to grow, or the result of a stimulation by substance that may be brought under therapeutic control.

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DISCUSSION

DR RICHARD W ROBINSON, LACONIA There is little doubt at some of the most dramatic recent occurrences in surgery from the symptomatic point of view, result from castration in advanced cases of carcinoma of the prostate. It appears from the literature that quite comparable results can be accomplished by the neutralization of these androgens through the constant and sufficient use of neutralizing trogen. We should not, however, lose sight of the fact that even in view of the quick relief these patients get from their symptoms, the problem of carcinoma of the prostate not solved by procedures of this kind.

Some months ago Randall reported the end results in 5 cases observed over a period of eight years in which castration had been done for carcinoma of the prostate and in which there were no cures, all the patients eventually dying of carcinoma. I believe that other similar results have been published, and I have recently heard presented facts that indicated that after a period of a year and a half to five years the carcinoma progresses in the usual manner or even sometimes in an apparently accelerated one. This being so one would certainly attempt to make a diagnosis of carcinoma with the hope of surgical cure.

Although carcinoma of the prostate, because of its location in the posterior lobe of the gland, does not manifest itself early by urinary symptoms, a yearly rectal examination of patients over the age of forty-five would reveal a great number of carcinomas that would otherwise remain unrecognized until it was too late even to consider a radical total removal of the prostate such as Young advocates.

One of the most interesting questions is why dramatic and quick relief is obtained not only from the pain but also and particularly from the obstructive effects of these large carcinomas. It does not seem possible that within the course of a week or ten days, as so often happens, any change in cellular structure or any regression of a carcinomatous mass could possibly take place. I wonder whether the explanation might not be that some change occurs in the vascular supply of the carcinomatous mass. Perhaps Dr Bowler or Dr Pedley can enlighten us on this phase of the subject.

Another interesting point is that there is more than one type of carcinoma of the prostate. Certain types particularly the small celled rapidly growing, malignant one, do not yield to the removal of androgens as do the majority of these growths. It will be interesting to find out whether carcinomas actually developed in the hypertrophied mass of adenomatous prostate yield to the removal of androgens in the same way as does carcinoma of the true prostate. There is considerable doubt whether the benign adenoma that develops in the center of it is of true prostatic origin.

DR ISADORE J ZIMMERMAN, Manchester Dr Bowler and Dr Pedley have made a valuable contribution to this meeting by reviewing the recent work on hormonal control in carcinoma of the prostate and by recounting their experiences during the past year. The discovery of the relation between the androgens and carcinoma of the prostate will always rank as an important milestone along the hard road toward the solution of this vexing problem.

My own experience with the use of castration and of stilbestrol has closely paralleled that of Dr Bowler and Dr Pedley. Clinical improvement is frequently apparent in a matter of days. Objectively the prostate becomes smaller and softer, but usually remains fixed and takes on a peculiar consistency that must be palpated to be appreciated. Thisologically there is actual degeneration of carcinomatous cells.

The effect of stilbestrol on the testis is of some interest in evaluating the mechanism of its eventual effect on prostatic carcinoma, in addition to its neutralizing effect on the androgens. With the co-operation of our pathologist, Dr Robert Biron I have been able to show that the administration of stilbestrol results in changes in the testicle resembling those found following irradiation.

Like Dr Bowler and Dr Pedley, I have not been willing to rely on stilbestrol alone but have given it following castration, hoping in this way to neutralize any androgens that might be elaborated outside the testis perhaps in the adrenal glands.

The subcapsular orchidectomy reviewed this morning is simple to perform, is not disabling and leaves the patient with a reasonably ornamental facsimile. I have found it perfectly easy to do both subcapsular orchidectomies through a single, small, linear scrotal incision.

I might say a word about the effect of regression in the size of the tumor following orchidectomy. The sphincter musculature of the bladder is involved in varying degrees by the carcinoma. Further regression of the tumor with orchidectomy following resection occasionally results in incontinence. It has been my practice therefore where feasible first to castrate the patient, and after the maximum amount of regression has occurred to decide whether tissue ought to be removed and if so how much of it.

It is obvious that, as has been pointed out today, in the short period of two years it is impossible truly to evaluate the long range significance of castration. To the great majority of these patients castration or stilbestrol or both unquestionably bring relief from symptoms and regression of the carcinoma and even of the metastatic lesions. It is therefore, with no intent to detract from the true value of this work and from the gratifying immediate results obtained in the vast majority of the patients that I re-emphasize what Dr Bowler and Dr Pedley have demonstrated in 2 of the cases reported. I refer to the universal experience of seeing with dismay the occasional resumption of the growth of the tumor after a period of latency, and also out and out failures. We must, therefore, temper our enthusiasm with the facts in so far as we know them as Dr Bowler and Dr Pedley have carefully done in evaluating this work. Further, we must continue to be on the alert for early cases of carcinoma of the prostate by doing a rectal examination routinely on every male patient over forty five years of age.

DR BOWLER (closing) There is little that need be added. It is obvious that one has to be extremely guarded to avoid overenthusiasm. On the other hand the subject is of great interest in connection with any biologic conception of malignancy, in that this is the first tumor occurring commonly in clinical practice in which one can observe and speculate on the relation of malignancy to glandular secretions.

There is no answer at the present time to Dr Robinson's question about the mechanism of the relief that these patients get from their dysuria. Dr Zimmerman in his discussion has explained the matter as well as it can be explained.

SOCIOECONOMIC ASPECTS OF DENTAL CARIES*

A Community and Individual Study of Dental Caries in Selectees

MAJOR ROBERT W. HYDE, M.C., A.U.S.†

WITH THE ASSISTANCE OF CORPORAL DANIEL J. O'CONNELL, A.U.S., AND CORPORAL GEORGE A. LENZI, A.U.S.

BOSTON

IN SPITE of the fact that the study of dental caries lends itself with ease to a broad social approach, comparatively little work has been done with this form of investigation. The examination of selectees for induction into the armed forces includes a dental examination and thus furnishes for study an excellent cross section of the nation's male population of military age. During the first year of induction, dental rejections were reported as the highest single cause of disqualification for military service, with approximately 9.4 per cent of those examined found to possess insufficient teeth to meet the minimum standards.¹ An almost identical high rate of dental disqualifications (9.3 per cent) was found at the Boston Induction Station during the only comparable period. Studies were instituted at this station to determine what community socioeconomic factors were influential in this situation, and it is the purpose of this paper to set forth the results of these studies.

Klein and Palmer² have presented an excellent study of the influence of community socioeconomic conditions on the incidence of dental caries in urban children six to fourteen years of age in New Jersey. The present study concerns a very different group. It appears that the differences in methods and material between the two studies are so wide that if significantly similar results were obtained, it would serve to validate the conclusions of Klein and Palmer that the intrinsic tendency of children to develop dental caries does not depend on the socioeconomic status of the community in which they live, and that the volume of dental care in the form of filling of permanent teeth increases markedly with a rise in community socioeconomic status.

Studies by Britten³ and Collins⁴ showed that frequency of dental service varies greatly with socioeconomic status. Such studies are important only when considered with others showing the variation in dental defects that require dental care, for certain groups with low economic status may not be seeking dental care for the reason that they do not need it.

In none of these studies has any correlation been made between the rate of dental caries and that of dental deficiency of such degree that the subject is unable to subsist on the Army ration. A consideration of the incidence of caries may be far different

from that of dental deficiency of such gross degree, wherein lack of reparative treatment rather than ability to resist caries may be the prime factor.

Classic studies made by Price⁵ and Pickerill⁶ have demonstrated the association of dental caries with the modern diet of civilized man and the almost complete absence of dental caries in all aborigines subsisting on native diets. Little has been shown, however, regarding the application of these studies to the variation in dental caries in the different races and nationalities now living in the United States.

It is not the purpose of this study to delve into the etiology of dental caries, but rather to present certain basic data necessary for the evaluation of preventive methods. Without knowledge of the relation of dental caries to community socioeconomic status and to nationality it is impossible to interpret findings on rates of dental caries.

SCOPE AND METHOD OF STUDY

The present study included the following factors: dental rejections in the examination of 60,000 consecutive selectees from twenty-one to thirty-eight years of age during the winter, spring and summer months of 1942; the decayed, missing and filled teeth in 3899 consecutive selectees from eighteen to thirty-eight years of age examined during a period of 1943; and the dental defects in foreign-born and first-generation Americans of the principal nationalities appearing in the examination of 2400 white and 1212 Negro selectees in a period of 1943.

The selectees were for the most part from urban backgrounds, since they came from the eastern segment of Massachusetts within about thirty miles of the seacoast. On the other hand, there were large enough areas beyond the large cities to make significant the number living in rural and semirural areas, such as would be found on Cape Cod.

The source of the selectees and the socioeconomic classification of the community from which they came were the same as those used in previous studies at this station of allergic states,⁷ tuberculosis⁸ and diabetes.⁹ Hence, the rejection rates of these medical conditions furnish controls for comparison with dental rejections.

The social study was made of each community (local board) from which selectees came, and those factors were evaluated that were considered to be indicative of socioeconomic level. These factors were medical care, educational facilities, social class,

*From the Boston Armed Forces Induction Station.

†Medical director, Medical Section, Headquarters Boston Armed Forces Induction Station.

recreational facilities, public works, undesirably crowded housing and the welfare rate per capita. Each community was given a score on the basis of each of these factors, and the total score was called its "desirability rating." Communities of similar desirability ratings were grouped, so that all the communities fell into a six-category scale of desirability from A in the finest communities to F in the slum areas. For a more complete description of this method of social analysis, the reader may refer to one of our previous studies.⁸

RELATION OF DENTAL REJECTIONS FROM MILITARY SERVICE TO COMMUNITY DESIRABILITY

The dental criteria for acceptance were relatively stable during the period in 1942 wherein 60,000 selectees were examined. For the greater part of the period the minimum requirement was an edentulous upper jaw and sufficient natural teeth in the lower jaw to support a partial denture.

The relation of the percentage of men rejected for military service to the desirability rating of the community from which they came is shown in Table 1. Although this relation is not entirely con-

sistent throughout the range, the percentage of disqualified persons ascends from 3.8 per cent in the best communities to 5.2 per cent in the poorest.

The factors that possibly explain the greater rejection rate in the communities of low socioeconomic standing are less reparative dental care, poorer personal dental hygiene and poorer nutrition. If, however, Klein and Palmer are correct in stating that the incidence of caries is the same at all socioeconomic levels, the increased rejection rate is due to lack of reparative dental care at the lower socioeconomic levels. Hence, it is necessary to know whether dental disqualification from military service is an index of the amount of dental caries or of lack of reparative dental treatment.

TABLE 1. Relation of Percentage of Those Disqualified for Dental Defects to Community Desirability Rating

COMMUNITY DESIRABILITY RATING	No EXAMINED	PERCENTAGE DISQUALIFIED FOR DENTAL DEFECTS
A	6,300	3.8
B	6,100	2.8
C	16,800	4.7
D	15,200	4.6
E	2,400	4.6
F	6,200	5.2

stant throughout the range, the percentage of disqualified persons ascends from 3.8 per cent in the best communities to 5.2 per cent in the poorest.

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RELATION OF TOTAL INCIDENCE OF CARIES PER PERSON TO COMMUNITY SOCIOECONOMIC STATUS

To ascertain the relation of total amount of dental caries to socioeconomic community status and thereby explain the true significance of dental disqualifications, a further study was undertaken wherein the number of decayed, missing and filled teeth per person was counted in selectees in each

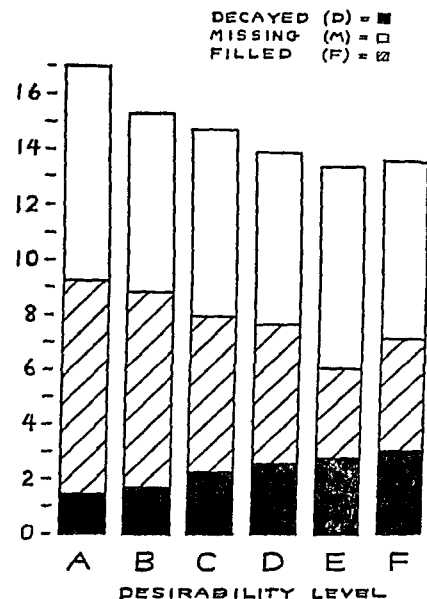


FIGURE 1. The Relation of the Incidence of Dental Caries to the Level of Community Desirability.

bars represent the number of decayed teeth per person found at the time of examination. There is an increase in decayed teeth from 1.5 per person in the best communities to over 3.0 in the poorest communities. Since it is obvious that a decayed tooth is evidence of lack of dental reparative care, it is clear that the need for dental care is present in all communities, but that in the poorest communities the need is twice as great as in the best ones.

The hatched segments indicate the number of filled teeth per person in each socioeconomic level. Here a striking contrast is shown, with about 8 filled teeth per person in the best communities decreasing to about 4 filled teeth per person in the poorest communities. Here can be seen the abundance of dental fillings in persons of every socioeconomic level and their increase with improvement of this level. The number of filled teeth per person appears to be a true representation of the variation in amount of

reparative dental care at different socioeconomic levels, so that it can be considered that dental care is twice as extensive in the best as in the poorest communities. This is in general agreement with the findings of Collins⁴ and of Britten,³ although they approached the problem from the angle of investigating the amount of care received. Our study, however, has the advantage of associating care received with the need for care.

The white segment represents the number of missing teeth per person from communities of each socioeconomic level. There is no significant correlation between the number of missing teeth and community desirability. Since in this respect our findings differ from those of Klein and Palmer,² it remains for further study to demonstrate whether any relation exists between the number of extracted teeth and socioeconomic status. It is certain that in communities where dental care is not easily available the patient prefers to have a tooth extracted to entering on any lengthy course of dental treatment.

The sum of the three segments of the bar represents the average amount of dental caries that each person has had,—that is, the total of decayed, filled and missing teeth,—and is called the "DMF." Here, quite strangely, the DMF per person in the best communities (17 per person) is greater than that of selectees from the poorest communities (14 per person). If this demonstrates conclusively that the average person in the best communities has had three more carious teeth than the average person in the poorest communities, the fact is of considerable importance. Before any such possibility can be accepted, however, two alternatives must be considered. In the first place, filled teeth may include many caries-free fissures that were filled and that would not have become carious. In the second place, the communities of low socioeconomic level contain a somewhat larger percentage of foreign-born and of races with better teeth than the American average.

If neither of these suggestions proves adequate to explain the increased incidence of dental caries in the better classes, it follows that: the supposedly superior nutrition of the better socioeconomic levels may be poorer nutrition from the dental point of view; that the more extensive personal dental hygiene practiced in the better communities may be injurious; and that the work of dentists may even be responsible for the increased DMF. Perhaps if the findings of Price⁵ and Pickerill⁶ that dental caries is experienced by civilized man on modern dietaries are considered, it can be assumed that the rating of socioeconomic level in this study conforms in some degree to civilization and that the best communities contain persons with more civilized modern dietary habits than those in Group F and hence with worse teeth.

It can at least be said that the people from poor communities have had no more dental caries than do

those from well-to-do communities. This conclusion and our findings on the relation of carious teeth and filled teeth to community socioeconomic level are in accord with the findings of Klein and Palmer.²

This study of the relation of DMF to socioeconomic level shows that dental requirements are so low that the rejections because of dental defects are more indicative of gross lack of reparative dental care than of the amount of dental decay. This shows that dental care is fulfilling a worthy role, but that the role is the repair of teeth, not the prevention of caries.

RELATION OF DENTAL CARIES TO NATIONALITY AND RACE

A study was made of the composition of each community (local board) by nationality. Only those communities were considered in this study wherein there was a predominant nationality. Although a community study of nationality has the intrinsic fault of including a minority of persons of other nationalities, it has the advantage of considering those of the same nationality who have grouped themselves and thus have preserved more of their original culture and habits, including dietary habits, than they would otherwise have done.

Table 2 represents the number of men disqualified for military service because of dental deficiency who resided in communities with a predominant nation-

TABLE 2. *Percentage of Persons Disqualified for Dental Defects from Communities with a Predominant Nationality.*

PREDOMINANT COMMUNITY NATIONALITY	No. EXAMINED	PERCENTAGE DISQUALIFIED
Irish	2440	6.8
English-speaking foreign and old American	1640	4.4
Italian	3472	4.1
Portuguese	2406	2.0
Jewish (Russian)	1869	1.9

ality in the first (1942) study of 60,000 examined selectees. In the Irish communities three times as many persons (6.8 per cent) were disqualified for military service because of dental defects as in the Portuguese (2.0 per cent) and Russian-Jewish communities (1.9 per cent). Since this is a far wider variation in dental rejections than that considered in Table 1, wherein the relation to socioeconomic status is considered, it becomes important to study dental caries in its relation to nationality. As has already been shown in the consideration of DMF and socioeconomic status, the variations in dental disqualifications according to nationality cannot be considered as primarily indicative of caries but rather as showing the proportion of persons with gross dental defects who have not had reparative dental care. With three times as many persons in certain communities as in others having dental deficiency of such a gross degree that it is disqualifying for military service, the need for community planning of dental care is suggested.

The study of the relation of the rate of dental caries to nationality differs from this community study of relation of dental rejections to dominant community nationality in that each person is of the nationality specified, so that there are included persons living in Americanized communities who have lost some of their national dietary habits.

Figure 2 shows the relation of decayed, filled and missing teeth and to nationality by parents' birthplace. A wide variation is seen in all factors. The

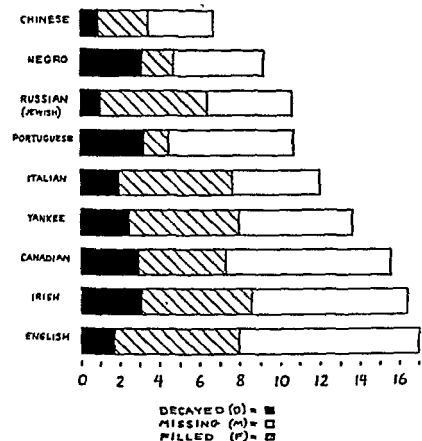


FIGURE 2. The Relation of the Incidence of Dental Caries to Nationality.

number of decayed teeth found at the time of examination ranged from an average of less than 1 per person in the Chinese and Russian (Jewish) groups to over 3 per person in the Irish and Portuguese groups. Here, the lack of relation of the number of decayed teeth found at time of examination (D) to the total number that had been decayed at some time (DMF) is especially noteworthy, with the Portuguese and Irish having had very different amounts of decay but nearly the same total number of decayed teeth (DMF).

The number of filled teeth per person also varied greatly with nationality. The Portuguese had the lowest number, 1 filled tooth per person; and the Negroes came next with less than 2 filled teeth per person. Both Negroes and Portuguese also had a comparatively high number of decayed teeth but a low number of teeth that had been attacked at some time by decay. Thus, two peoples with extremely inadequate dental care, as shown by such a high rate of decayed teeth and low rate of filled teeth, had far less dental decay than the average. This again shows that the nationalities having the least dental care may have the least dental caries. Most of the other groups had high numbers of filled teeth: Russian (Jewish), Italian, old American, Canadian,

Irish and English all having on the average more than 4 filled teeth per person.

The number of missing teeth per person appears to bear a rough relation to the number of teeth that have at some time decayed (DMF). It decreases from a high rate of 8.5 missing teeth per person in the English, with a DMF of 17.0 to 3 per person in the Chinese, with a DMF of 6.5. No relation can be seen between missing teeth and either decayed or filled teeth. The only nationality wherein there was a comparatively large number of missing teeth was the Portuguese, with 5.8 missing teeth per person and a low DMF (10.5). This may possibly be explained by the fact that many of the Portuguese come from rural Cape Cod areas, where dental care may be less accessible or the cultural background may be comparatively low.

The total amount of caries that each person had ranged from over 15.5 per person in the English, Irish and Canadians to 10.5 in the Portuguese and Russian (Jewish), 9.5 in the Negroes and 6.8 in the Chinese. As has already been shown in comparing the numbers of decayed and of filled teeth, the total amount of caries is independent of dental care. This wide difference in dental decay in different nationalities is important because it shows the insignificant place of dental care in dental decay and presents a valuable angle of attack on the problem of etiology of dental caries. Furthermore, it shows that prevalence figures must be corrected on the basis of nationality.

For explanation the factors of both heredity and culture require consideration. Either there is an inherent difference in racial susceptibility to caries or there is a difference in the dietary habits of the different races.

Price⁶ and Pickerill⁶ have established beyond doubt that the teeth of aborigines, almost perfect while on their native dietary, become carious when they change to the modern civilized dietary. This suggests that the element of racial susceptibility is entirely secondary to dietary habits, although further study may be required to demonstrate this conclusively.

SUMMARY

Studies were made of dental defects found in the examination of selectees at Boston Armed Forces Induction District and the relation of dental defects to nationality and the socioeconomic background of the communities from which these selectees came.

The incidence of total caries (decayed, missing and filled teeth) per person was found to be highest in the best communities and lowest in the poorest, whereas the number of filled teeth decreased consistently from the best to the poorest communities, reflecting the consistent effect of socioeconomic status on reparative dental care.

The fact that more men from the poorer communities than from the best ones were rejected for

insufficient teeth is more indicative of lack of reparative care than of the amount of dental decay that they had had.

The English and Irish had had the greatest amount of dental decay, whereas the Negroes and Chinese had the least. This fact was not dependent on dental care, since the English had a great number of filled teeth and a small number of decayed teeth, whereas the Negroes had a large number of decayed teeth and few filled teeth. Three times as many selectees from Irish communities were rejected because of dental defectiveness as from Portuguese or Russian (Jewish) communities.

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IN VITRO ACTION OF SULFAMERAZINE, PHTHALYLSULFADIAZINE, PHTHALYL-SULFAMERAZINE AND PHTHALYLSULFATHIAZOLE ON ENTERIC PATHOGENS

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THE sulfonamides have produced clinical results beyond expectation. These drugs were first directed against the septicemias, especially streptococcal and pneumococcal infections. The attention of investigators later centered on infections due to other bacteria, notably those of the pathogenic intestinal group. Relatively little work has been done on the direct effects of the sulfonamide drugs on intestinal bacteria and most of the available literature deals with their clinical effects. The preponderance of clinical studies is justified and is the most important consideration for both patient and practitioner.

In most conditions where the sulfonamides are employed, the blood level of the drug—usually administered by mouth—if kept at a satisfactory concentration for the desired time seems to be responsible for the beneficial effects. The ability of a drug to be absorbed from the intestine in an amount sufficiently high to maintain a proper blood level is especially noted in diseases where a septicemia or bacteremia is manifested. This is particularly true in infections with streptococci, pneumococci, meningococci and the like.

The situation is different when one considers the possible effects of these drugs in infections where the gastrointestinal tract is the main site of the disease or pathologic changes. In such cases one may differentiate two large groups of intestinal diseases: those in which bacteria responsible for the disease are restricted to the intestinal wall, no bacteremia occurring at any time and those in which, in addition to the local intestinal changes, a bacteremia occurs

more or less regularly during certain stages of the disease. No discussion will be attempted of the question whether one has to deal in these cases with a primary bacteremia and a secondary localization in the intestinal wall, or whether primary localization occurs in the intestine and is followed by bacteremia.

In the first group, where bacteria are confined to the intestinal wall, the resultant diseases are caused by the different Shigellas or by *Vibrio comma*. In the group where bacteremia occurs regularly, they are produced by members of the typhoid-paratyphoid group, *Eberthella typhosa* and the Salmonellas. The infrequent intestinal infections with *Bacillus anthracis*, with the Brucellas, with *Pasteurella tularensis* and with *P. pestis* should theoretically be included in the latter group.

It is apparent that the effects of the drugs on these dissimilar groups of enteric infections must depend on entirely different qualities inherent in them. If the bacteria are restricted to the intestinal tract, it is more appropriate to choose drugs that have a slow rate of absorption and remain in the intestine in effective concentration. In the second group, drugs must overwhelm the bacteria in the intestine as well as in the general circulation. Here, a drug with good but not too rapid absorption should be chosen, or even a combination of two different drugs may be administered. One of these should be easily absorbed, thus combating the bacteria in the circulation, whereas the other should be poorly absorbed, thus acting on bacteria in the intestinal lumen and wall.

Aside from the problem mentioned in the preceding paragraphs, the action of the various sulfonamides on the separate pathogenic bacteria should be known in detail. Owing to mutual chemical affinities, even

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slight changes in the composition of a given drug may alter its effects on various bacteria; it may become more useful in the destruction of one bacterium and less useful in that of another. It is fully realized that any conclusions drawn from the following experiments can cover only one — and perhaps not the most important — part of the story. Investigations made *in vitro* enable one to determine the immediate effect of a given drug on a given bacterium, but do not decide which drug is most useful clinically in a given disease. The questions of rapid or slow absorption, of producing and maintaining an appropriate blood level and of the rate of drug excretion cannot be solved by test-tube studies.

Experiments of this type may, however, prove useful in cases where several sulfonamides of similar absorption rates are available. They may be especially useful when performed with those pathogenic bacteria that exert their principal or exclusive action on the intestinal tract. So far as the intestinal diseases are concerned, there is apparently no unanimity of opinion concerning which sulfonamides should be used in combating the particular pathogenic bacteria involved.

According to the literature, there is no doubt whatsoever that some sulfonamides are effective against the dysenteric infections. It seems, however, that in infections with bacteria of the typhoid-paratyphoid group the effects of such drugs are not proved, since some difference of opinion on the subject exists.¹⁻⁶ These doubts, together with other reasons, account for the preparation of numerous new sulfonamides in the hope of finding a new compound that will prove effective in cases in which the older drugs have failed. This is laudable work, and any opportunity to evaluate a new drug and to determine its worth against certain bacteria is most welcome. We are therefore indebted to Dr. E. L. Burbidge of Sharp and Dohme, Incorporated, Philadelphia, for supplying us with four new sulfonamides.

So far as we know, only one of these drugs, sulfamerazine, is under clinical investigation; a few reports of its use have already appeared.⁷⁻¹⁵ A similar sulfonamide with two methyl groups, sulfamethazine, has been tested clinically by three groups of investigators, with results comparable to those obtained with sulfamerazine.¹⁶⁻¹⁸ Nothing has as yet been published on the other three drugs. These preparations were obtained during studies on several older well-known compounds for their effects on various enteric organisms. References in this paper are restricted to *in vitro* studies made against the intestinal organisms.¹⁹⁻²³

The opportunity has thus been given to compare the effects of the new drugs on certain bacteria with the effects of the older drugs from which they are derived. At the present time all that will be done is to state briefly what the *in vitro* effects of the new drugs are on representative species of intestinal bacteria. Perhaps this will serve to expedite clinical applications that may follow.

MATERIALS AND TECHNIC

The chemical structures of the drugs at our disposal were as follows:

Sulfamerazine is sulfa-methyl-pyrimidine or 2-sulfanilamido-4-methylpyrimidine. It is monomethylated sulfadiazine, but has some characteristics peculiar to the specific compound. Tests show that it is more readily soluble, more quickly and more fully absorbed and less rapidly excreted than is sulfadiazine.⁸

Phthalylsulfamerazine is sulfamerazine to which a phthalyl radical has been added.

Phthalylsulfadiazine is sulfadiazine to which a phthalyl radical has been added.

Phthalylsulfathiazole is sulfathiazole to which a phthalyl radical has been added.

These drugs are crystalline white powders, sparingly soluble in water. Solutions were prepared in sterile nutrient broth. In no case was it possible to obtain clear solutions above a concentration of two per cent. Even at this concentration sulfamerazine and phthalylsulfathiazole did not dissolve readily unless the container was gently heated. In a few cases it was found necessary to heat the stock solution just before use because of a slight amount of sedimentation. It occurred to us that heating might increase the concentration of the drug to a slight extent, but we believed the increase to be negligible. We attempted to minimize this effect by preparing only small amounts of the drugs at a given time.

Since it is known that the solubility of sulfonamides in water — and consequently in nutrient broth — increases with a rising pH, working with strong basic solutions would have been advantageous. But the alkalinity of the solutions was limited by the fact that the medium had to be favorable for bacterial growth. It was decided to maintain a pH of 7.6 in all dilutions throughout the course of the experimentation, using a few drops of 10 per cent sodium hydroxide to aid solution of the drug and to obtain the proper reaction. Lower concentrations were prepared by diluting the 2 per cent solution with necessary amounts of nutrient broth at pH 7.6. Routine solutions were concentrations of 2.0, 1.5, 1.0, 0.50, 0.25, 0.10, 0.05, 0.025 and 0.010 per cent.

The following bacteria were tested in these series: *Escherichia coli*, *Eberthella typhosa*, *Salmonella paratyphi*, *S. schottmülleri*, *S. enteritidis*, *S. suispestifer*, *Shigella dysenteriae* (Shiga), *Shig. paradysenteriae* var. *Flexner*, *Shig. paradysenteriae* var. *Hiss* and *Shig. sonnei*. A standard loop of each bacterium was taken from a twenty-four-hour slant on agar, transferred into 5 cc. of nutrient broth (pH 7.6) and incubated for twenty-four hours. The degree of cloudiness after this period of time varied with each organism.

In order to have approximately the same number of bacteria in all tubes, the twenty-
were standardized with a

elometer tubes were originally standardized against a twenty-four-hour growth of *E. typhosa*. By plating out and counting the ten different strains, it was determined that the nephelometer reading for *E. typhosa* could be used as well for the standardization of the other nine organisms, the percentage of error being practically zero. Consequently, all twenty-four-hour broth cultures were standardized against a tube of the nephelometer corresponding to a count of 16,000,000 bacteria per cubic centimeter. Some slight errors are possible in this method of standardization, but it was thought certain that a few thousand

were found among the separate trials never exceeded one tube higher or lower in concentration and were exceedingly rare.

DISCUSSION

Several results are apparent from Table 2. Sulfamerazine is effective against *Esch. coli* in vitro in a concentration of 2 per cent; the other three drugs are bactericidal only at concentrations above 2 per cent. The same drug is bacteriostatic for this organism at a concentration of 0.1 per cent, whereas the others fall between 1 and 2 per cent.

Phthalylsulfathiazole is the best bactericide against *E. typhosa*, being effective at 1.5 per cent, and it is bacteriostatic at 0.5 per cent. The other drugs range in bactericidal power from 2.0 to over 2.0 per cent, and in bacteriostatic effect from 1 to over 2 per cent. The superiority of phthalylsulfathiazole over the other three drugs is fully evident.

Against *S. paratyphi* phthalylsulfathiazole is bactericidal at 2 per cent, with the other drugs going above that concentration. For bacteriostatic action, both sulfamerazine and phthalylsulfadiazine are effective at 1 per cent, whereas the others are effective above 1.5 per cent.

Sulfamerazine is the most effective bactericide against *S. schottmülleri*, killing at 2.0 per cent, and together with phthalylsulfathiazole is effective as a bacteriostatic agent at 1 per cent.

Sulfamerazine and phthalylsulfadiazine are equally effective as bactericides against *S. enteritidis* at 1.5

bacteria more or less would in no way alter the results of the experiments. The findings obtained in the series later proved this assumption to be correct.

A 1:100 dilution of each standardized suspension was made in physiologic saline solution just prior to use. One tenth of a cubic centimeter of this dilution was added to 0.9 cc. of the respective drug dilution, so that each tube always contained the same number of bacteria (16,000 per cubic centimeter). All tubes were incubated for twenty-four hours and read for degree of cloudiness. Following this, appropriate dilutions of the growth were plated out on Endo's agar. After a few preliminary trials it was learned which dilutions were satisfactory in order to obtain a countable number of colonies on the plates. One tenth of one cubic centimeter of the respective dilution was always plated out, two plates being streaked with the same glass rod. In this manner there was regularly obtained a countable number of colonies on at least one of the plates after incubating them for twenty-four hours. As a control, a similar amount of bacteria was inoculated into 0.9 cc. of broth and twenty-four hours later plated out in the manner described above. It was thus possible to discover by comparison any slight bacteriostatic effect of the drug concerned. A sample protocol is shown in Table I.

EXPERIMENTAL RESULTS

The experimental findings are listed in Table 2. The percentage noted in each column reveals the lowest concentration of the respective drug that produced the indicated effect. Each figure represents the average of ten complete trials. Any differences that

per cent. Together with phthalylsulfathiazole, all three are bacteriostatic at 0.1 per cent.

Against *S. suispestifer* the best bactericide is phthalylsulfathiazole (1.5 per cent). The best bacteriostatic agents are sulfamerazine and phthalylsulfadiazine (0.5 per cent).

TABLE 1. Sample Protocol.

Organism: <i>E. typhosa</i>		Drug: Phthalylsulfathiazole		Protocol: 36	
Tubes inoculated: 2-2-43				Plates made: 2-3-43	
CONCENTRATION OF DRUG	CLOUDINESS OF TUBES	DILUTION USED	ENDO COUNT PLATE 1	COUNT PLATE 2	
%					
2.0	Clear	Whole	0	0	
1.5	Clear	Whole	0	0	
1.0	Trace (?)	Whole	60	0	
0.50	Trace	1:1000	225	0	
0.25	Moderate	1:2000	575	90	
0.10	Moderate	1:2000	810	200	
0.05	Heavy	1:4000	Innumerable	1220	
0.025	Heavy	1:4000	Innumerable	1270	
0.010	Heavy	1:4000	Innumerable	1230	
None (control)	Heavy	1:4000	Innumerable	1250	

TABLE 2. Bactericidal and Bacteriostatic Action of the Sulfonamides on Various Intestinal Bacteria.

ORGANISM	ACTION	SULFA-MERAZINE	PTHALYL-SULFADI-AZINE	PTHALYL-SULFAMER-AZINE	PTHALYL-SULFA-THIAZOLE
		%	%	%	%
<i>Esch. coli</i>	A	2.0	2.0+	2.0+	2.0+
	B	0.1	1.5	2.0	1.0
<i>E. typhosa</i>	A	2.0	2.0+	2.0+	1.5
	B	1.0	2.0	2.0+	0.5
<i>S. paratyphi</i>	A	2.0+	2.0+	2.0+	2.0
	B	1.0	1.0	2.0+	1.5
<i>S. schottmülleri</i>	A	2.0	2.0+	2.0+	2.0+
	B	1.0	2.0	2.0+	1.0
<i>S. enteritidis</i>	A	1.5	1.5	2.0+	2.0
	B	0.1	0.1	0.5	0.1
<i>S. suispestifer</i>	A	2.0+	2.0	2.0+	1.5
	B	0.5	0.5	2.0	1.0
<i>Shig. dysenteriae</i>	A	0.1	0.5	1.0	0.5
	B	0.05	0.1	0.1	0.1
<i>Shig. paradysenteriae</i> var. <i>Flexner</i>	A	1.5	1.0	2.0	0.5
	B	0.05	0.1	0.1	0.05
<i>Shig. paradysenteriae</i> var. <i>Hiss</i>	A	2.0	1.0	2.0+	2.0+
	B	1.0	1.0	2.0	1.0
<i>Shig. sonnei</i>	A	1.5	1.0	2.0	1.5
	B	0.5	0.5	1.5	0.5

A = bactericidal concentration (complete destruction of bacteria).
B = bacteriostatic concentration (partial inhibition of growth as compared with control tube).

Each of the various strains of *Shigella* differs with respect to the bactericidal and bacteriostatic actions of the four drugs studied. The Shiga strain is destroyed by sulfamerazine at 0.1 per cent, the same drug being effective as a bacteriostatic agent at 0.05 per cent. The Flexner strain is killed by phthalylsulfathiazole at 0.5 per cent; the same drug, and also sulfamerazine, are bacteriostatic as low as 0.05 per cent.

A concentration of 1 per cent phthalylsulfadiazine proved to be bactericidal for the Hiss and Sonne strains, but the highest bacteriostatic effects are equally divided among sulfamerazine, phthalylsulfadiazine and phthalylsulfathiazole. These three drugs are bacteriostatic for the Hiss strain at 1 per cent and for the Sonne strain at 0.5 per cent.

From the results obtained on four hundred experiments with these four drugs and by comparison with the eight hundred protocols already obtained on the older sulfonamides, the following conclusions may be readily drawn:

Sulfamerazine is better than sulfadiazine when used in vitro against *S. enteritidis*, *S. suispestifer* and the Shiga and Sonne strains of *Shigella*. Sulfadiazine is a better bactericidal and bacteriostatic agent than is sulfamerazine when used against *E. typhosa*, *S. paratyphi*, *S. schottmülleri* and *Esch. coli*. Both drugs have similar bactericidal and bacteriostatic effects on the Hiss and Flexner strains of *Shigella*. The addition of the methyl group to sulfadiazine therefore makes it more effective chiefly against the dysentery organisms, but weakens its actions against some of the others in vitro.

Phthalylsulfadiazine is better than sulfadiazine when used against *S. enteritidis* and the Hiss, Flexner and Sonne strains of *Shigella*, but the reverse is true when these drugs are used against *E. typhosa*, *S. paratyphi*, *S. schottmülleri*, *S. suispestifer* and *Esch. coli*. Both drugs are equally effective against the Shiga strain. The addition of the phthalyl radical to sulfadiazine makes it more effective for most of the dysentery organisms and for *S. enteritidis* in vitro.

Sulfamerazine is decidedly better as a bactericide and bacteriostatic agent than is phthalylsulfamerazine against all the organisms studied. The addition of a phthalyl group to this particular drug diminishes the effective action of the sulfamerazine in vitro.

Phthalylsulfathiazole has a better bactericidal action than has sulfathiazole when used against *E. typhosa* and the Flexner strain of *Shigella*; it is also a better bacteriostatic agent against *S. enteritidis*. As bactericides both are equally effective against *S. enteritidis*, *S. suispestifer* and *Shig. sonnei*. Against *Esch. coli*, both paratyphoid species and the Hiss and Shiga strains of *Shigella*, phthalylsulfathiazole is much weaker, both as a

bactericide and a bacteriostatic agent, than sulfathiazole.

The tabulation indicates that the best bactericidal and the best bacteriostatic effects on each organism examined are not always produced by the same drug. It is also apparent that, at least in vitro, the addition of the phthalyl group serves some limited advantage with sulfadiazine and sulfathiazole against certain bacteria. It actually diminishes the effective power of sulfamerazine for all bacteria studied. This observation, of course, does not necessarily mean that the actions in vivo are also lessened by the addition of the phthalyl radical. Since the attached radical is easily split from various compounds,²⁹ it is most likely set free in vivo, so that the end effects may be identical with those produced by the simpler sulfonamides. This question can be answered only by animal experimentation.

The results were obtained by testing one strain only of each of the organisms, otherwise the technical work would have extended beyond the facilities at our disposal. Helmholz²⁹ has shown for *Esch. coli* that different strains of this organism exhibit different resistances against concentrations of the same drug in urine. Possibly by testing more strains of a single type of organism the results would have been slightly altered. Since some of the differences demonstrated were so striking and so constant, however, we believe that the results may be considered valid.

SUMMARY

Four new sulfonamide drugs — sulfamerazine, phthalylsulfadiazine, phthalylsulfamerazine and phthalylsulfathiazole — were tested for their in vitro action on certain enteric pathogens.

From the results obtained, it is apparent that, as with the older sulfonamide compounds, the *Shigellas* are more susceptible to bactericidal and bacteriostatic action in vitro than are strains representative of other genera.

In certain instances, the new compounds were found to be more effective in vitro than the older compounds, whereas in others, the reverse was found to be true.

We are indebted to Miss Marian Land for technical assistance furnished during these studies.

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MEDICAL PROGRESS

HEMATOLOGY

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DURING war, research in subjects not directly connected with military medicine must naturally become greatly restricted. Because of this, publications in the field of hematology have been fewer in number, but many of these are of immediate practical value. In line with these new conditions, this year's review will be limited to a discussion of three subjects: blood transfusions and blood substitutes, hemorrhagic diseases and hemolytic processes.

BLOOD TRANSFUSIONS AND BLOOD SUBSTITUTES

The Russian Contribution

Bagdasarov¹ reviews the development of the Russian system of blood storage and distribution, in many respects the forerunner of the blood and plasma banks of today. Perhaps realizing the imminence of a new world conflict, the Russians in 1927 set up the Central Institute for Blood Transfusion in Moscow, with separate decentralized institutes in various cities. By 1932, eighty of these institutes were in active operation for the distribution of blood to the surrounding communities and for active research in methods for the preservation, administration and storage of fresh and cadaver blood. The Spanish Civil War served as a perfect setup for the clinical application of these studies. It was found

that a mixture of citrate and glucose was a better preservative than citrate alone, that the universal donor could be used on a large scale in the front lines without further typing or cross matching, and that undue hemolysis in transportation could be prevented by the use of isothermic containers, which were best transported by the airplane rather than by truck or train. The use of plasma in Russia has lagged behind that in this country and Britain, perhaps because every available soldier and noncombatant at or close to the fighting zone has served as a volunteer donor. The red-cell mass, a by-product of plasma preparation (see below), has been routinely used in cases of severe hemorrhage. A somewhat mysterious note in Bagdasarov's review is that regarding "physiological balanced solutions," which contain a certain amount of plasma in an alcohol-and-glucose-solution base. This cocktail-like infusion is said to reinforce the vital processes, especially when the wounded patient suffers from disturbed hemodynamics not associated with severe blood loss and in septic cases. Although not strictly apropos, mention may here be made of the development by Bogomolets² of A. C. S. (anti-reticular cytotoxic serum), with spleen and bone marrow used as antigenic substances. The resulting serum injected in small doses is said to enhance greatly the immune activities of the reticuloendothelial cells and thus help such diverse conditions as frostbite, slowly

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healing infections, typhus fever and many others. Bogomolets also believes that it may reduce the normal aging process.

Blood Groups, Agglutinins and So Forth

Methods. The use of high titer serum, which is now readily obtainable, should be routine. Serum concentrates,³ powdered serum* and serum and plasma fractions⁴ are all being developed and have their specialized indications. Powders keep well in a wide temperature range and give an extremely quick reaction that can be readily seen on the slide with the naked eye. Since the globulin fraction of serum or plasma contains all the enzymatic factors and antibodies, including agglutinins, methods for its separation from the albumin fraction have been developed. Thus, Pillemer⁵ precipitates the albumin with methyl alcohol and concentrates the globulin fraction; the agglutinin content of this material is extremely high. This work has been continued in the laboratory of Dr. E. J. Cohn at the Harvard Medical School under contract with the Committee on Medical Research of the Office of Scientific Research and Development and in collaboration with the Division of Blood Research, Army Medical School.⁶

The slide test is adequate for ordinary typing, but it should not be relied on for cross-matching purposes, since it is relatively insensitive, particularly for weakly reacting and "warm" agglutinins, including the anti-Rh agglutinin. As emphasized in previous reviews, the Landsteiner-Levine test-tube technic is far more accurate and should become a routine procedure.

Under this method, small test tubes (7 by 75 to 100 mm. — that is, Hinton or Kahn tubes) are used. One drop of the serum to be tested, 2 drops of a 2 per cent red-cell suspension and 1 drop of normal salt solution are placed in the tube, mixed and placed in the incubator remaining there for at least thirty minutes. The tube is removed and centrifuged at extremely slow speed for one minute. The "button" may be examined with a hand lens for the presence or absence of agglutination. The tube is then shaken and examined for macroscopic agglutination. Confirmation of the presence or absence of agglutination is obtained by examination of some of the tube's contents on a slide with the low power of the microscope. This method, although seemingly complicated in its description, is readily performed in simple laboratory setups and is sufficiently sensitive for the detection of the great majority of normal and abnormal agglutinins of low titer, including the anti-Rh agglutinin.

The one possible disadvantage of the routine use of the above technic is that it fails to detect cold agglutinins, which have recently assumed some diagnostic importance. This disadvantage may be obviated by performing simultaneous compatibility

tests at either room or, preferably, icebox temperature. For routine transfusions, it matters little whether the recipient's blood contains a cold agglutinin, provided that relatively warm blood is used; however, the finding of incompatibility owing to the appearance of agglutination in the slide-cross-matching technic at room temperature has often held up the use of transfusion in patients desperately ill with acute hemolytic anemia.

Rh agglutigen and anti-Rh agglutinin. The development of knowledge regarding the Rh factor (agglutigen) and its relation to transfusion reactions and to acute hemolytic anemia of the newborn (erythroblastosis fetalis) has made one of the most fascinating and important chapters in modern medicine. This has been duly recorded in previous reviews. The correctness of Levine's original assumption that erythroblastosis fetalis is due to the development by an Rh- mother of an anti-Rh agglutinin, with resultant effects on the fetus's Rh+ cells, has been borne out in at least 90 per cent of all cases. Other agglutinins, or even such physical factors as the condition of the placenta, may have some bearing in a few cases. The failure of some infants born of Rh- Rh+ matings to develop acute hemolytic anemia may depend on the father's genotype: that is, an Rh+ phenotype is made up of either genotypes RhRh or Rhrh. From the latter genotype, the infant may inherit either dominant Rh or recessive rh. If the latter, the union of recessive gene rh with the mother's rh results in an Rh- infant's blood.⁶

The low incidence of erythroblastosis fetalis in Negroes and Chinese led Levine and Wong⁷ to study the incidence of the Rh factor in these groups. Although 15 per cent of Whites are Rh-, only 5 to 8 per cent of the Negroes tested were Rh-, and only 1 of the 150 Chinese tested was Rh-. (It should be pointed out to those who pride themselves on the lack of the "monkey" factor in their red cells that its absence does not necessarily preclude the possibility of the presence of, say, a baboon or an orangutan factor. Studies of human blood for such factors have not yet been undertaken.)

Determination of the Rh factor is of importance in at least three conditions: in pregnancy and childbirth when a transfusion is contemplated for severe anemia or shock, in acute hemolytic anemia of the newborn and in repeated transfusions. In the last if the recipient is Rh-, repeated transfusions of blood, even of the same group, will almost certainly result in the development of an anti-Rh agglutinin; thus, after three to six or more transfusions, the next transfusion if consisting of Rh+ blood may result in a severe and perhaps fatal hemolytic reaction.⁸

For determination of the Rh factor, a potent anti-Rh serum must be available. As yet, such serums are difficult to obtain, because the regular production of potent anti-Rh agglutinin in animals has proved

*Prepared by Lederle Laboratories, Incorporated, Pearl River, New York.

extremely difficult and because high-titer anti-Rh serums are only occasionally found in the mothers of infants with erythroblastosis fetalis. It is advised that each mother of such an infant be routinely tested for anti-Rh agglutinin and that if this is present, even at low titer, she be bled 50 to 100 cc. Concentration of serum can later be performed. Methods for doing this are now in process of development.

The test for the Rh factor is performed by the Landsteiner-Levine technic at 37°C., as above described. It is important to use dilute — 1 to 2 per cent — red-cell suspensions. Levine⁶ and his co-workers have found three types of anti-Rh serum, one agglutinating 87 per cent of the red cells of white persons (anti-Rh₁ and anti-Rh₂), another agglutinating 85 per cent (anti-Rh₁) and the third agglutinating 73 per cent (anti-Rh₂). Since the last serum gives 27 per cent negative reactions, the significance of an Rh— determination in a given case is open to doubt. Thus, unless a laboratory has a highly potent anti-Rh testing serum, it is important to perform a careful compatibility test of the recipient's serum with the prospective donor's red cells. To do this, the time of incubation should be prolonged to one hour. Boorman, Dodd and Mollison⁹ suggest a modification of Levine's technic, which they state brings out more clearly the anti-Rh agglutinin. These workers allow the mixture of recipient's serum, donor's red cells and normal salt solution to remain in the incubator for two hours. The pattern of the sediment is then examined with a hand lens and a portion is pipetted off for microscopic examination. They state that the manipulation of the blood involved in centrifugation and shaking may abolish a weak reaction. If such tests are negative, the transfusion may be given with almost complete safety. The reservation must nevertheless be made that even with a completely negative *in vitro* test, there may be an *in vivo* hemolytic reaction. The only possible way to obviate this completely is to set up a list of well-established Rh— donors for use in the three conditions referred to above — that is, in women in childbirth, in cases of erythroblastosis fetalis and with repeated transfusions. It is almost essential to use nothing but Rh— blood in infants with acute hemolytic anemia, since transfusions are the only treatment, and the introduction of Rh+ cells may result in the combination with any still present anti-Rh agglutinin derived from the mother.

Cold hemagglutinins. The antigen-antibody reaction between human red cells and serum that is observed chiefly or solely at temperatures below 20°C. is called "cold hemagglutination." Cold agglutinins in low titer are commonly present. Thus, Kettel¹⁰ found them in 95 per cent of normal subjects, and more recently Shooter¹¹ in examining 4710 serums observed that 32 per cent showed these antibodies at 5 to 7°C. Cold agglutinins sufficiently strong to be active at room temperature were found,

however, in only 29 of 10,000 serums. Low temperatures at times activate or bring to light an otherwise weak agglutinin; this is reminiscent of the Donath-Landsteiner phenomenon — the activation by cold of the abnormal hemolysin of paroxysmal cold hemoglobinuria. The subject of cold hemagglutination is an old one, having been discussed by Landsteiner in 1903 and more fully by Landsteiner and Witt in 1926.* Although cold hemagglutinins have been observed in such diverse diseases as cirrhosis of the liver, hemolytic anemia of the acquired type and infections due to spirilla and trypanosomes, interest in this subject has been considerably enhanced in the past year by the finding of such agglutinins of high titer in primary atypical (virus ?) pneumonia.^{13,14} The initial hope that this antibody would prove of diagnostic importance in the differentiation of atypical and other pneumonias has proved only partially correct, since a fairly high titer is present initially in only about 50 per cent of all cases. The titer of agglutinin frequently increases with progression of the disease and may not reach its peak for seven to twenty-one days.¹⁵

The cold hemagglutinin appears to be quite distinct from the normal blood agglutinins, since it agglutinates all human red cells, even those of Group O, and may agglutinate those of a number of animals — that is, "pan-agglutinin." Because it also has the property of agglutinating the red cells of its own blood, — at least in the test tube, — the term "autoagglutinin" has often been used. This, however, is only partly descriptive and it is probably best to use the more general term "cold hemagglutinin."

Aside from its purely diagnostic significance, the cold hemagglutinin has recently assumed considerable clinical importance. Thus, certain cases of acute hemolytic anemia occur at times in association with primary atypical pneumonia. Usually the sulfonamide drugs have been administered and it has been customary to ascribe the hemolytic reaction to the drug. Whether or not this is correct, when a transfusion is considered for the severe anemia and blood-grouping tests are done, it is often found that all prospective donors are incompatible. This is of course due to the presence of a cold agglutinin in high titer with resultant agglutination — at room temperature with the ordinary slide technic — of the red cells of all blood groups. For this reason, transfusions have often been delayed or not given at all in patients desperately needing them. In such an event, the matter is quickly resolved by performing the cross matching at incubator temperature by the test-tube technic described above. I¹⁶ have also recommended in such cases the use of blood that is kept warm from the time of its removal from the donor to its entrance into the blood stream of the recipient.

*For an excellent review of the entire subject of the cold hemagglutinins the reader is referred to an article by Stats and Wasserman.¹²

The cold hemagglutinin in these cases is also important from the standpoint of chilling of the patient. Thus, marked acrocyanosis and beginning gangrene of the nose, ears and fingertips have been recently described in association with primary atypical pneumonia and a high titer of cold agglutinin.¹⁷ The cold agglutinin may persist for months¹⁸ or perhaps years following an attack of atypical pneumonia, making the person who harbors it liable to the development of hemoglobinuria, chronic hemolytic anemia, extreme coldness and blueness of the extremities or even gangrene on exposure to extreme cold. In a case under study at the present time, all these symptoms have been present since an attack of pneumonia two years ago.¹⁸ Two or three further attacks have occurred in the interim. The cold hemagglutinin is present in a titer of 1:128,000. Because of the presence of a chronic hemolytic anemia with splenomegaly, it is likely that this patient has considerable *in vivo* autoagglutination, which is enhanced by exposure to cold. Stats and Bullowa¹⁹ report a somewhat similar case in which symmetrical gangrene of the tips of the extremities occurred with exposure to cold. This patient did not have a hemolytic process, but the *in vivo* agglutination of red cells could be demonstrated by introducing ice water into the conjunctival sacs and examining the bulbar and palpebral conjunctivas with the slit-lamp corneal microscope.

From these and other observations several conclusions may be drawn. First, patients with primary atypical pneumonia should under no circumstances be chilled. Second, if a transfusion becomes necessary because of an acute hemolytic reaction, the cross matching should be done by the test-tube technic at incubator temperature. Third, warm blood should be used and the apparatus, tubing and so forth should be kept constantly as warm as possible. Cold blood withdrawn from the refrigerator should not be used, certainly not before proper warming.

Transfusion Reactions

Severe and often fatal transfusion reactions still occur all too frequently. Exact statistics on their incidence are almost impossible to obtain because most of them go unreported. They are probably as frequent as they are because blood grouping is often relegated to inexperienced persons with little awareness of the great responsibilities involved in correct typing and cross matching. The development of a fatal transfusion reaction in a relatively healthy young person who is being prepared for an elective operation is a tragic event that is in many cases due to omission of either the typing or the cross-matching test. Each transfusion should be preceded by careful cross matching of the recipient's serum with the prospective donor's red-cell suspension and by typing of both the recipient and the prospective donor. Except under very special circumstances, it is not

necessary to do the so-called "minor agglutination" — that is, the donor's serum versus the recipient's red cells. If the same blood groups are used, no agglutination with the donor's red cells will occur. If a Group O donor, for example, is used for a Group A recipient, the resultant agglutination with the donor's red cells is to be expected because members of Group O have anti-A and anti-B agglutinins in their serums.

As noted above, cross matching should preferably be done by the test-tube technic at incubator temperature and for at least thirty minutes. This has recently been made an official recommendation of the (British) Medical Research Council.²⁰ If an unusual emergency exists and thirty minutes seems too long a period to wait, blood plasma should immediately be given.

A transfusion reaction is best treated by its prevention. The intern or technician who performs the test must be acutely aware of the important responsibility involved — literally one of life and death. Even in an emergency, carelessness and too much hurry are inexcusable. Even with all precautions carefully observed, a severe reaction occasionally occurs, that is, the *in vivo* biologic test is at times more accurate than any form of *in vitro* testing. For this reason, the recipient should be carefully watched, particularly during the administration of the first 50 to 100 cc. of blood. If there is any complaint whatever of pain in the back or flanks, pain down the legs, a smothering sensation, a burning sensation in the face, a sense of constriction, a chilly sensation or chill or even a sense of something wrong, the transfusion should be immediately discontinued. These symptoms are usually indicative of intravascular agglutination. Whereas the recipient can usually survive the administration of 50 to 100 cc. of incompatible blood, the agglutination of 500 cc. of blood is usually fatal. The investigation of the causes of a severe hemolytic transfusion reaction is described by Mollison.²¹

Red Cells from Bank Blood

The great developments in the use of plasma resulted in almost complete ignoring of the mass of red cells, which were almost routinely discarded. Many observers, however, have remarked on this great waste in a valuable by-product, and in recent publications suggestions for its use have been made. The British workers MacQuaide and Mollison²² and Williams and Davie²³ used the red cells for the treatment of anemia. Bagdasarov,¹ the director of the Russian Central Institute for Blood Transfusion, reported in 1942 that the red-cell mass was best preserved at 4 to 6°C. with a solution containing magnesium sulfate, potassium chloride and sodium chloride; no marked change in red cells occurred up to twelve days. The red cells were found of great value in cases of severe anemia following blood loss. Watson²⁴ pointed out that by the use of a

cell suspension one could rapidly increase the oxygen-carrying capacity of the blood with a minimum of introduced solution. This was particularly useful in ambulatory patients and in certain cardiac patients with anemia. Alt²⁵ stated that the main value of red-cell transfusions is to increase the erythrocyte count in patients with anemia, particularly following severe hemorrhage. Other suggested uses are in patients with severe iron deficiency and in progressive refractory anemia — that is, in cases with bone-marrow disease due to aplasia, leukemia, tumors and so forth. Because red cells in suspension may be given in concentrated form, larger numbers of them can be given at one time and more frequently than with the use of whole blood. Litwins²⁶ has suggested the use of Group O red cells admixed with pooled plasma to form a completely universal Group O blood — that is, one containing no agglutinogens and more or less completely neutralized agglutinins.

A new use for preserved red cells — the promotion of normal healing — was suggested by Moorhead and Unger.²⁷ Seldon and Young²⁸ state that such red cells either from a single or from different blood groups, when mixed together and stored in a refrigerator for days or weeks, form a gelatinous mass that may be used as a dressing material for wounds, burns, ulcers and chronic infections. This was found of distinct value in the promotion of growth of vascular and connective tissue in the injured surfaces. Because of the difficulty of keeping the semiliquid red-cell material in contact with the wound, Seldon and Young dried it and used it as a fine sterile dusting powder applied directly to the wound surface. Infected wounds, poorly healing postoperative abdominal wounds, certain proctologic cases, varicose and other ulcers of the leg and amputation stumps have been successfully treated. The method seems to offer distinct possibilities in the treatment of healing wounds.

Because of these two developments, the formerly discarded red-cell by-products of the blood bank are now of distinct value; this applies to the treatment of severe anemia, particularly when the regenerative capacity of the bone marrow is impaired, and in the promotion of better wound healing.

Blood Substitutes

Liquid plasma. Liquid plasma when prepared under completely aseptic precautions has been stored at room temperature for a year and a half or longer.²⁹ During this time, it loses none of its protein or colloidal osmotic value, but there is a rapid loss of antihemorrhagic factors, such as prothrombin, and of complement. Newhouser and Lozner²⁹ state: "The permissible temperature range of preservation probably lies between 15 and 30°C. (59 and 86°F.). Below this range excessive fibrin precipitation may occur, and above this range protein denaturation occurs rapidly."

The chief advantage of pooled liquid plasma is its ready availability. It may be taken off a shelf and without further testing, reconstituting or other steps be given immediately to a patient in shock. The intravenous set should contain a suitable filter to hold back particles of fibrin. The chief disadvantage of liquid plasma is that it is an excellent culture medium for the growth of bacteria; hence, unless plasma is scrupulously prepared, preserved and tested for sterility, it may well become infected.

Plasma may be given in so-called "units" of 250 cc. each; the recent tendency has been to give larger doses than 1 unit. Thus, 4 units (1000 cc.) may be given without danger, although due consideration should be given to the relatively large amounts of sodium and citrate that are introduced. A caution against the too liberal use of citrated blood was recently voiced.³⁰ Citrate may be quite toxic, although the toxicity depends to some extent on the rate of injection. Five grams of citrate given intravenously may be considered as a safe maximum, since 15 gm. has been shown to be fatal. Since 50 cc. of a 2.5 per cent solution (1.2 gm.) is customarily used for 1 unit of plasma, this indicates that more than 4 units of plasma, or 1000 cc., should not be used. A citrate reaction³¹ which may result in tetany owing to the binding of calcium, is characterized by the development of a positive Chvostek sign, a general tingling sensation, dilatation of the pupils and, finally, actual clonic twitching. The reaction can be quickly terminated by the intravenous injection of calcium chloride or gluconate.

Frozen plasma. Liquid plasma may be preserved in the frozen state in special refrigerators that maintain a constant temperature of -15 to -20°C. Under such conditions, there is indefinite retention of the various thermolabile constituents of the plasma. Reconstitution from the frozen state requires about thirty minutes at a temperature of 37°C., the bottle being placed in a water bath, not an incubator. According to Newhouser and Lozner,²⁹ the best results in thawing are obtained by this method, followed by maintenance for two to three weeks at room temperature. Quick thawing may be followed by a cloudy plasma.

The chief advantages of frozen plasma lie in the maintenance of sterility and the preservation of immune bodies and antihemorrhagic and other factors. The sterility factor alone has been emphasized as of the greatest importance. The disadvantages of freezing lie in the use of a special, rather expensive freezing unit; the necessity for slow reconstitution (thawing), making it imperative to wait for at least thirty minutes, sometimes a long time in an emergency; and the occasional breakdown of current or apparatus, with consequent thawing. These disadvantages can all be obviated by appropriate measures, some of which are covered by Newhouser and Lozner.

Dried plasma. This material, prepared by dehydrating liquid plasma by one of several processes, can be quickly reconstituted by the addition of pyrogen-free distilled water. It contains in unaltered form both albumin and the various thermolabile globulin constituents of the previously liquid plasma and, what is more, preserves them for many months without appreciable loss of activity. It has a wide range of safety with regard to temperature and bacterial contamination. It should not, however, be allowed to freeze or to stand for any length of time at a temperature above 55°C.²⁹

The unusual value of dried plasma in shock and cerebral accidents was quickly recognized: it could be reconstituted in relatively small amounts of fluid, thus obtaining a hypertonic material which would draw unusual amounts of plasma into the circulation and simultaneously dehydrate certain swollen tissues, such as an edematous brain. The use of two-times, four-times and five-times concentrated plasma has been advocated as a routine measure by various investigators. With twice-concentrated plasma, 250 cc. of water can be used to reconstitute the dried material obtained from 500 cc. of plasma. This is probably more effective in shock than is isotonic plasma, and furthermore adds to the circulation at once an adequate amount of protein. Four-times or five-times concentrated plasma possesses the diluting function in even greater fashion than the twice-concentrated material. Erf and Jones³² dissolve the dry material obtained from 500 cc. of whole blood in 60 cc. of water, which is given by syringe rather than by gravity, as is customary when amounts over 50 or 60 cc. are used. They claim that this is a far quicker and more readily available method, especially for use on the battlefield, than is the gravity-tubing-filter method. Heyl and his collaborators³¹ state that the viscosity of concentrated plasma because of the presence of the globulins is much greater than that of concentrated albumin (see below). The total osmotic pressure is furthermore greater because of the presence of concentrated electrolytes; however, the colloid osmotic pressure is less than that of concentrated albumin solutions.

Thus, dried plasma has many advantages: its availability at almost any temperature; its elasticity with reference to the amount of solution that need be added, thus allowing complete control of the degree of desired colloid osmotic pressure; and its retention of sterility under almost any conditions. Its possible disadvantages lie in its use in too highly concentrated form: here if the patient is dehydrated, there may be further drying of various tissues while the blood volume is becoming increased. Furthermore, in a patient with myocardial involvement, the rapid increase in blood volume may impede the circulation.

Dried plasma has its greatest usefulness in shock and related states. It is of value in other conditions as well: in hypoproteinemia, especially with edema, to add protein; in certain conditions of local edema,

as in the brain and the extremities, when other methods of therapy have failed; in chronic or acute nephritis as a diuretic, even in the absence of hypoproteinemia; and in severe hepatitis, particularly in the presence of a reduced blood protein and ascites. It would probably be even more widely — and perhaps unwisely — used in civilian practice than it is at present were it less expensive. Sufficient dried plasma for the military services has fortunately been supplied by volunteer donors, with the invaluable assistance of the Red Cross and of various pharmaceutical houses.

Human albumin. Plasma is a highly complex solution. It not only contains proteins that are essential for its own stay in the circulation but has all the various hormones, enzymes, metabolites and so forth that are in process of transportation from one tissue to the others. It has been customary to divide the plasma proteins roughly into two fractions: albumin and globulin. The albumin fraction is relatively pure, but the globulin fraction is composed of a large number of substances that differ greatly from one another with respect to their chemical structure and their function. Although great strides have been made in studying these complex proteins, it is probably safe to say that thus far only the surface has been scratched. Two of the important tools in studying the plasma proteins are the Tiselius apparatus for the observation of electrophoretic mobilities and the ultracentrifuge.

The task of purification and fractionation of human and animal plasmas for military use has been undertaken by the Department of Physical Chemistry at the Harvard Medical School, under the direction of Professor E. J. Cohn. Disregarding respiratory, hormonal and enzymatic proteins, the plasma proteins may be divided according to Cohn³⁴ into those concerned with clotting of the blood, with complement, with immune processes, including antibody and antitoxin, and with water and electrolyte balance. Among those that have thus far been identified are fibrinogen and prothrombin and the "mid-piece" and the "end piece" of complement. The bulk of the various globulins comprising the globulin fraction of plasma has thus far not been separated in pure form; they have been characterized either as α -globulins or pseudoglobulins or — in terms of their electrophoretic mobilities — as α , β , and γ globulins. In general, the globulins have an extremely high molecular weight and on that account exert a smaller osmotic pressure than do the smaller molecules of albumin. The separation in relatively pure form of the simpler albumin fraction from the complex globulins has been effectively accomplished by Cohn and his collaborators.³⁴

The albumin thus prepared and freed from the more labile and more readily denatured fibrinogen and globulins is readily soluble in water, yielding clear solutions even at concentrations containing as much as 70 per cent of albumin by volume. Even in

concentrated form, albumin solutions have a lower viscosity than has plasma, interact only slightly with other proteins and salts and stand up under conditions of extreme heat and cold.²⁹ They furthermore exert a much greater colloid osmotic pressure than does whole plasma. For these reasons and because of their immediate availability for intravenous injection, albumin solutions have proved extremely useful in the treatment of wound shock. The standard Army-Navy package of concentrated human-albumin solution consists of 25 gm. of albumin in 100 cc. of buffered salt solution, supplied in a large ampule ready for instant injection by gravity through an ordinary 19-gauge or 20-gauge needle.²⁹

Heyl, Gibson and Janeway³³ have calculated that each gram of albumin injected intravenously adds by osmotic pull 18 cc. of fluid to the circulation. These calculations, when subjected to actual experimentation in the human subject, were found to be surprisingly accurate; thus, the actual increment in plasma volume varied from 13.2 to 24.0 cc. in all experiments, with an average value of 17.4 cc. The use of 25 gm. of albumin is thus approximately equivalent to the administration of 450 cc. of normal circulating plasma or 500 cc. of citrated plasma as usually prepared.

Hence, a concentrated solution of purified albumin possesses many advantages. Certain disadvantages must also be assessed. Because of its very great osmotic pull, there is a danger of dehydrating vital tissues, especially in soldiers and others who have been exposed to many hours of struggle under conditions of extreme heat and thirst. For this reason, the use of albumin solutions should probably be restricted to hydrated or only slightly dehydrated persons. Another disadvantage of albumin solution is its lack of globulin substances and thus of enzymes, blood coagulating materials and antibodies. The administration of several injections of albumin solution has furthermore been found to result in a modification of the albumin-globulin pattern of the plasma, with possible effects on immune reactions.³⁵

Indications for albumin solution are thus relatively few, and depend entirely on its great colloidal osmotic pull. It is useful in shock and in conditions associated with hypoproteinemia and edema. As yet, it is not available for civilian use; even if it were, its cost would probably render its use almost prohibitive. Partly for this reason and also because of ready availability, the preparation of albumin from animal sources has been given much thought.

Bovine albumin. Cohn and his collaborators³⁴ have shown that human albumin and bovine albumin present remarkably similar molecular patterns from a physiochemical point of view. Both by means of the ultracentrifuge and the Tiselius electrophoretic apparatus, the two albumins are to all intents and purposes indistinguishable. The chief difficulty, however, is not the physicochemical one but rather the immunologic reaction. This probably develops

because of slight contamination of albumin with globulin. The matter of development of sensitivity to a heterologous material is of great importance and has been studied by Janeway³⁶ and by Heyl, Gibson and Janeway.³³ The latter authors came to the following conclusion: "No statement regarding the safety for intravenous use of crystallized bovine serum albumin of low globulin content can be made until more extensive clinical tests have been completed in order to determine to what extent and under what circumstances it will be safe to use a protein of animal origin for therapy in man."

Sites of Administration of Blood and Blood Substitutes

The preferred site of administration of whole blood, plasma, and the various blood substitutes is naturally in the various large veins, which are usually readily found in the antecubital fossas. In extreme shock and in extensive burns, these veins may either be collapsed or inaccessible. It is well, therefore, in emergencies to have in mind the possibility of administering these substances in other than the basilic veins.

The femoral vein is not customarily thought of in this regard, but its use might well be increased. The vein is extremely large and is situated just medial to the femoral artery, which is readily palpated in the inguinal region. With a little practice, puncture of the vein is readily performed. Administration of plasma by this route was found extremely useful by the Boston City Hospital group during the Coconut Grove fire disaster in 1942.

The infusion of blood and other fluids by way of the sternal marrow was suggested by Tocantins³⁷⁻³⁹ in 1940 and has gradually assumed increasing value. Tocantins demonstrated by careful injection experiments in cadavers, and later by clinical studies in animals and human beings, that substances injected into the marrow cavity are immediately taken up into the venous circulation apparently unchanged. In adults, the marrow cavity of the sternum is readily entered by the introduction of a sternal-puncture needle—an abbreviated stiff lumbar puncture needle will do—through the skin and subcutaneous tissue and through the anterior lamella of the sternum. The procedure, which is done under novocain anesthesia, is a simple one and is readily learned. A sensation of give is felt when the needle enters the marrow cavity. The stilet is then withdrawn and a small amount of marrow is aspirated. An adapter may be attached to the needle and to rubber tubing and a gravity device, or the blood or fluid may be introduced under positive pressure by means of a syringe. If the injection of more than 50 cc. is contemplated, it is wise to use a two-way stopcock and thus avoid removing the syringe from the needle for each 50 cc. As Tocantins states, rapid injection—over 20 cc. per minute—may be accompanied by a sense of pressure or grinding pain.

similar to that of angina pectoris, this quickly disappears at the termination of injection. It is, however, rarely necessary, or even advisable, to inject fluids at such a rapid rate. The use of the intrasternal route is particularly applicable to military medicine, and a number of reports from military establishments in which its use is favorably commented on have appeared.⁴⁰⁻⁴¹ In one such report, the sternal-puncture needle was allowed to remain in situ for three or four days, with occasional cleaning, 14,000 cc of blood and fluid was given with no untoward effect.

The marrow may also be used for the introduction of fluids and blood into the infant's circulation. Tocantins's studies have shown that in the newborn and in early infancy the marrow cavity either above or below the knees is best utilized. In older children, aged two to four, the mid-tibia may be better. Above the age of four, the sternal cavity is fairly well developed and thus available for injection.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

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CASE 30171

PRESENTATION OF CASE

A fifty-nine-year-old housewife entered the hospital because of a bearing down sensation in the pelvis.

The patient was in good health until three months before admission, when she noticed "something falling into the vagina" whenever she stood up or walked around. On examining herself she found a small lump in the vagina. These symptoms persisted. She had had no nocturia, vaginal discharge, incontinence, increased frequency or bleeding.

She had had tuberculosis at twenty-nine and passed five years in a sanitarium, at which time she had a phrenectomy. At fifty she had a pulmonary hemorrhage and stayed in bed for two years. She had had a right nephrectomy for renal tuberculosis eight years prior to admission. She had had occasional indigestion over a period of many years without known nausea, vomiting or diarrhea. The menopause occurred at fifty-one.

Physical examination showed a well-developed, obese woman in no distress. There was dullness over the right lung posteriorly and over the left apex, with coarse rales throughout. The heart was normal. Tenderness was elicited over the nephrectomy scar. Pelvic examination showed a rectocele and a cystocele.

The blood pressure was 150 systolic, 75 diastolic. The pulse was 100; the temperature and respirations were normal.

Examination of the blood was normal. The urine was normal. A blood Hinton test was negative.

X-ray examination of the chest showed evidence of inactive tuberculosis in both lungs. An intravenous pyelogram showed a normal left kidney. The right kidney was absent.

On the fourth hospital day a vaginal hysterectomy and a perineal repair were performed. After the first ten minutes there was a fall of blood pressure to 120 systolic, 60 diastolic, and although the patient had a little unusual bleeding, she withstood the operation well. The pathological diagnosis on the uterus was leiomyomas of the uterus and chronic endocervicitis with endocervical polyp. On the

*On leave of absence.

second postoperative day the temperature rose to 101°F. She had considerable nausea and belching, without any vomiting. She was given intravenous fluids for two days and 2 gm. of sulfadiazine daily for nine days. The nausea and belching persisted, and the temperature remained at about 100°F. She had some fullness and a questionable mass in the left lower quadrant. On the tenth postoperative day the hemoglobin was 10.7 gm. per 100 cc. An x-ray film of the chest showed no change from the previous examination. On the twelfth hospital day she was propped up and felt very weak and dizzy. She was still quite nauseated and belched a great deal. She began to complain of anorexia and of distress in the left upper quadrant. Examination of the blood on the seventeenth hospital day revealed a red-cell count of 2,180,000, with 6.6 gm. of hemoglobin, and a white-cell count of 11,400, with 71 per cent neutrophils. In the course of the next two days she vomited coffee-grounds material, which was strongly guaiac positive. The prothrombin time was 22 seconds (normal, 22 seconds). She was given several transfusions. The vomiting subsided, and the red-cell count was 2,500,000, with 7.1 gm. of hemoglobin.

A gastrointestinal series on the twenty-second postoperative day showed a hiatus hernia that measured about 9 cm. in diameter (Fig. 1). The mucosa in the hernia and in the adjoining subdiaphragmatic part of the stomach appeared somewhat widened, but no ulcerations were seen. The hernia was observed to change in size and shape. The remainder of the stomach and the duodenum were normal. There was a laminated, calcified gallstone 8 mm. in diameter in the region of the gall bladder. Following the gastrointestinal series, she had several massive gastrointestinal hemorrhages with bright-red blood in the stools and in the vomitus. She was given nineteen transfusions each consisting of 500 cc. of whole blood, and large amounts of intravenous fluids. She continued to bleed, however, and died on the twenty-ninth postoperative day.

DIFFERENTIAL DIAGNOSIS

DR. ARLIE V. BOCK: It would be interesting to know what the blood findings were. Was the hemoglobin done at the time of the first blood examination?

DR. BENJAMIN CASTLEMAN: It is not recorded.

DR. BOCK: I should like to know whether any stools were examined to indicate whether she was losing blood.

DR. CASTLEMAN: If so, they are not recorded.

DR. BOCK: To go over this briefly, I should say that, in view of the subsequent events, the pelvic condition and the operative procedure probably had nothing to do with the major underlying cause of death. She had a long history of tuberculosis. I

presume that diagnosis is correct in view of the time she was observed in a hospital. The fact that after some twenty years of good health she had a recurrence of the tuberculosis, as indicated by the pulmonary hemorrhage and presumably other signs that are not mentioned, and the fact that she had a nephrectomy, presumably indicate that the diagnosis of tuberculosis had been carefully gone into before the latter step was taken. So I think we can

is usually quite silent. A gastrointestinal disorder with such a hernia usually is infrequent, but when it does occur is characteristic, with a story of difficulty with swallowing or trouble when in the upright position, often relieved by lying down. If the patient bends over, especially to the left, there may be a sensation of something being squeezed up into the chest. There are usually odd sensations of that kind, none of which were present in this case.



FIGURE 1. Roentgenogram Showing the Hiatus Hernia

dismiss the problem of tuberculosis in this case. Some amyloidosis might be found, but I do not believe it could be extensive in this well-nourished woman, and I do not know that it could have had anything to do with hemorrhage anyway.

What are the causes of this type of extraordinary hemorrhage, so severe as to cause death and coming on following the operative procedure that I said I doubted had anything to do with the underlying trouble? The first and obvious thing is the description of the hiatus hernia. The history of bleeding given here, if it has anything to do with hiatus hernia, is decidedly atypical. We know that the usual type of bleeding is oozing for weeks or months, with the development of a secondary anemia, and then subsiding, with gradual recovery from the anemia. Then a secondary period of oozing starts and secondary anemia again develops. The history

The indigestion that is mentioned may very well have been due to the presence of cholecystitis and stone

May I see the x-ray films?

DR. MILFORD SCHULZ: These films merely demonstrate what has already been said in the protocol. Here we have the large hiatus hernia, an unusually large one; apparently it is not paraesophageal, from what can be seen here. There is no evidence of a lesion elsewhere in the stomach or duodenum.

DR. BOCK: In this hospital we have seen many cases of hernia of the stomach much larger than this one.

I should have supposed that if the bleeding in this case were due to hernia, there would have been more history of indigestion, more suggestion of secondary gastritis and much more history of bleeding with a resultant anemia, which would have announced it-

self to the patient by fatigue, palpitation and all the things that go with such an anemia. In view of the fact that the history is silent with reference to this hernia, I am inclined to rule it out as the cause of the bleeding. It is certain that some of these patients have massive hemorrhages and even bleed to death. I suppose that the mechanism of such bleeding is increased venous pressure in the part of the stomach above the diaphragm. There are no ulcerations of the mucosa that bleed. At post-mortem examination this part of the stomach is quite red from congestion, and the part below the stricture pale and normal. But in the present case, with this type of massive bleeding and a silent history, I doubt that the bleeding came from the hiatus hernia.

The next thing that one should consider is the presence of a peptic ulcer. If one rules out hiatus hernia and associated gastritis as the cause of bleeding, then ulcer is the next commonest cause of this type of bleeding, but there is nothing in the history to suggest it. That may not be important, since hemorrhage is often the first sign of ulcer in many cases. I am also influenced by the fact that the duodenal cap is described as normal. Hence, I am inclined to rule out ulcer.

Another possibility is cirrhosis of the liver. There is no history to suggest it; but, again, massive hemorrhage may be the first presenting symptom of cirrhosis of the liver. On the evidence we have here, I cannot rule it out.

Was the serum protein done?

DR. GORDON DONALDSON: No.

DR. BOCK: The dye retention test?

DR. DONALDSON: No.

DR. BOCK: We have no evidence either clinically or from the laboratory data to confirm the diagnosis of cirrhosis, and yet I think it cannot be ruled out and I have to consider it seriously as a cause of this woman's death, with bleeding from esophageal varices.

Did she have a nonvisualized leiomyoma of the stomach? We have made mistakes in the past, when we found nothing by x-ray examination, in assuming that bleeding of an extensive sort in the gastrointestinal tract was due to the presence of an unvisualized ulcer. That is a serious mistake, and because leiomyoma may be present, we should not be satisfied to treat a patient who is bleeding and has had bleeding on a number of occasions by assuming that the diagnosis is one of peptic ulcer. A leiomyoma may be responsible for severe hemorrhage and may cause repeated hemorrhages before anything positive is found by x-ray examination. We have nothing here to support such a diagnosis except the history of hemorrhage.

Judging from the cases of hiatus hernia that I have seen I am inclined to rule this lesion out as the cause of bleeding. I do not believe that the patient had an ulcer. I think that the diagnosis is cirrhosis of the liver or, less likely, leiomyoma. Amyloid disease

may have been found. Without a gastroscopic examination, there is nothing to help in the diagnosis of gastritis.

DR. LELAND S. MCKITTRICK: Does the bright blood that she passed by rectum bother you at all, Dr. Bock, in accepting a lesion of the stomach or esophagus as the source of the bleeding?

DR. BOCK: It does not say how much, but I believe the hemorrhage was considerable and came very rapidly; I still think it was a high hemorrhage.

DR. DONALDSON: Preoperatively, we directed all our efforts toward ruling out tuberculosis as a contraindication to doing anything to the prolapse. The chest and kidney situation was evaluated, and I must say that it was not until after she had bled postoperatively that we got a story of indigestion. She said she had had indigestion only when she was in the tuberculosis sanitarium. On bed rest, she developed indigestion, but never had any nausea or vomiting. We did not discover that she was bleeding until the eighth postoperative day, when we propped her up and found that she was dizzy. She was a fat and sallow woman, and we did not appreciate that she was anemic. On rechecking, we found that the hemoglobin level was surprisingly low, several stools were guaiac positive. We perhaps made a mistake in doing the gastrointestinal series, because following that she bled profusely.

DR. MCKITTRICK: Dr. Donaldson asked me to see this patient in Dr. Arthur W. Allen's absence. She presented quite a problem. Concerning the x-ray examination that Dr. Donaldson tends to doubt his judgment on, I should like to take issue with him on that point, because I think that he was right. It is important to know from where a patient is bleeding, particularly if there is a question of operation. If a definite ulcer could have been demonstrated, this woman would have been operated on with a reasonable chance of surviving the operation. The absence of a demonstrable ulcer, which, as Dr. Bock has said, does not exclude it, makes it less likely and possibly changes the method of approach. So I feel that an x-ray is worth the risk that it may incur in unexplained gastroduodenal bleeding.

Of course the problem was to control the bleeding. The patient had bled massively, or at least she lost a lot of blood. It came from the gastroduodenal region. We thought that it probably did not come from a duodenal ulcer. The bleeding was more massive than that which occurs from hiatus hernia; but knowing that massive bleeding occasionally does arise from that source, we thought that that was probably the answer and we treated her on that basis.

I felt much disturbed about this patient, and I thought that I had let down both Dr. Donaldson and Dr. Allen in not having advised operation. There was one thing in the history that I should have paid more attention to. When a patient bleeds

massively as this patient did we have a right on a logical basis to assume that the bleeding is coming from a large artery. It would be unusual for a diffuse process such as one ordinarily associates with a hiatus hernia to bleed a patient out as promptly as this patient did bleed out. That is rather characteristic of bleeding from a large single vessel, such as occurs in a posterior duodenal ulcer. Therefore, it seemed to me, after this patient had got to the point where we could not operate on her, that I had "missed the boat," in that she probably had a fairly extensive ulceration of a vessel that might have been amenable to surgical attack. By the time I had convinced myself that that might have been the answer, it was too late to do anything about it. She was not a good operative risk. If we had operated, and if she had nothing that we could get at directly, she probably would never have got off the table.

Dr. BOCK: I think that Dr. McKittrick's reasoning is good, but a patient can have massive hemorrhage and bleed to death from hiatus hernia with secondary gastritis. Ordinarily one finds oozing blood from this lesion, with repeatedly positive stools; the patient usually recovers, even though nothing is done about it.

Dr. McKITTRICK: If I had known of patients dying under the circumstances that you describe, I should probably have felt differently than I did

Dr. BOCK: I think that you are correct. I* first became interested in this problem in 1928, when my first case was explored because I could not believe that the bleeding was due to hiatus hernia. The second case had already been explored by the late



FIGURE 3 Drawing of the Interior of the Herniated Portion of the Stomach Showing the Large Ulcer with the Bleeding Vessel.

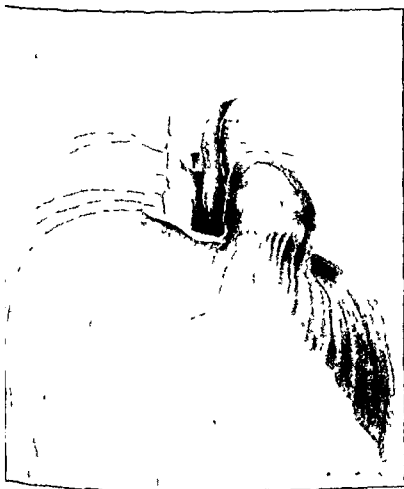


FIGURE 2 Drawing of the Hiatus Hernia in Situ.

In the law of chance, a rapid depletion must be more frequent from a single vessel than from the type of thing that you are talking about, and sometimes one has to gamble on what is likeliest.

Dr. Daniel F. Jones, who would not believe that the bleeding was due to a hiatus hernia, but we later proved that such was the case.

Dr. CASTLEMAN: But ordinarily one finds that the bleeding has occurred over a long period of time?

Dr. BOCK: Yes; and usually there is a silent history. I cannot believe that this patient bled from the hiatus hernia.

CLINICAL DIAGNOSES

Hiatus hernia.

Gastritis, with massive hemorrhage.

Dr. BOCK'S DIAGNOSES

Cirrhosis of liver, with bleeding from esophageal varices?

Leiomyoma of stomach?

Old pulmonary tuberculosis.

ANATOMICAL DIAGNOSES

Diaphragmatic hiatus hernia, with bleeding from ulcer of herniated portion of stomach.

Operation: vaginal hysterectomy and repair, recent; right nephrectomy, old.

Pulmonary tuberculosis, bilateral, inactive.

*Bock, A. V., Dulin, J. W., and Brooke, P. A. Diaphragmatic hernia and secondary anemia, ten cases. *New Eng J Med* 209 615-625 1933

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy showed a definite hiatus hernia (Fig. 2). The hernial sac was made up only of pleura and peritoneum, there being no diaphragmatic muscle in that region. The portion of the stomach that was present within the hernia contained a shallow ulcer measuring 4 by 3 cm. (Fig. 3). In its center was an eroded artery, which was the source of the bleeding. We were able to follow that artery back to the gastric artery, which arose from the celiac axis. Microscopic study of the ulcer showed that it did not have the fibrinoid base of a peptic ulcer, but that it was simply necrosis of the mucosa and muscularis mucosa, with a granulation-tissue base. Although the portion of the stomach within the hernia was easily reduced at autopsy, it must have been partially constricted for some time. There was a moderately severe gastritis around the ulcer.

DR. MCKITTRICK: Do you think that the lesion could have been recognized at exploration?

DR. CASTLEMAN: I believe that the hernia could have been reduced at operation, following which you certainly would have been able to feel the ulcer and probably the pouting bleeding vessel, such as you do in dealing with a posterior duodenal ulcer.

CASE 30172

PRESENTATION OF CASE

A twenty-three-year-old man was admitted to the hospital because of rectal bleeding.

The patient was in excellent health until about twenty months before admission, when he had severe diarrhea lasting four or five days and consisting of ten or more stools a day. There was intermittent, crampy, generalized abdominal pain, especially on the right. The diarrhea subsided except for two episodes, each lasting for one week and occurring three and ten months after the first attack. The crampy pain was present before, during and after the attacks. Ten months before admission he enlisted in the Army, where he underwent basic training for two months. He then had another attack of crampy, low abdominal pain and diarrhea, for which he was hospitalized. With a bland diet the diarrhea subsided but the pain persisted. A gastrointestinal series and Graham test were negative. A barium enema showed a constricting lesion of the right colon. X-ray films of the chest, examination of the sputum and gastric washings for tubercle bacilli and a tuberculin test were negative. Operation was advised, but he requested, and was granted, medical discharge. Following discharge his condition remained the same. One week before admission he had a small gush of bright-red blood following an otherwise normal bowel movement. He

had had no chills, fever, nausea, vomiting, night sweats, loss of appetite or change in weight. No other gastrointestinal or genitourinary symptoms were noted.

Physical examination showed a well-developed, well-nourished man in no distress. The heart and lungs were normal. An abdominal mass was palpated on the right side by one or two examiners. There was no tenderness or spasm.

The blood pressure was 110 systolic, 78 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 5,760,000, with 86 per cent hemoglobin. The white-cell count was 12,500. The urine was normal.



FIGURE 1. Roentgenogram following Postevacuation Barium Enema.

A blood Hinton test was negative. The stools were dark brown, with a ++++ guaiac test. The non-protein nitrogen was 27.5 mg. per 100 cc., the protein 6.9 gm. per 100 cc., and the chloride 102 milliequiv. per liter. A proctoscopic examination showed a normal rectum.

A plain film of the abdomen revealed gas in the ascending and transverse colon and a small amount of gas and feces in the descending colon, but no gas in the rectum. An intravenous pyelogram was negative. A barium enema showed ready filling of the descending and transverse colon up to the hepatic flexure, at which point the bowel was markedly narrowed for 10 cm. (Fig. 1). Proximal to this, the

cecum did not fill easily. The wall was irregular, but without any change in the mucosal pattern except for shelf formation and small ulcerations. The chest films were negative. A Miller-Abbott tube was passed into the small intestine.

On the tenth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES G. MIXTER: I think that, at once, one comes to the conclusion from the history of crampy, generalized, abdominal pain, the change in his bowel function, the blood by rectum, and the presence of a probable mass in the right side of the abdomen, as well as the x-ray findings, that we are dealing with a gastrointestinal lesion probably of the large intestine, but possibly of the small intestine.

May we see the x-ray films?

DR. LAURENCE L. ROBBINS: This is the lesion, approximately 8 cm. in length, in the ascending colon extending nearly to the hepatic flexure. The lumen appears to be narrowed to about 2 or 3 mm. in diameter—perhaps 5 mm. at its widest portion. I do not believe that one can be absolutely sure of ulceration, but certainly the possibility is suggested. One thing that does appear to me more significant than is expressed in the report is that the margins are not typically "shelf-like" and seem to change the least bit in the various films. There is absence of the normal mucosal pattern. The chest is negative.

DR. MIXTER: That does not correspond with the usual spool-like type that one would associate with cancer of an obstructive nature.

DR. ROBBINS: Not typically.

DR. MIXTER: From these findings we can rule out the other systems, and limit our consideration to the intestinal tract.

As I read this over, there came to mind, of course, the different lesions that I associate readily with three of the factors here—namely, the probable mass, the presence of blood, substantiated by one episode of bright-red bleeding and the ++++ guaiac test, and the x-ray findings. I can remember years ago as an intern here, when Dr. Maurice Richardson would see a case with an obscure diagnosis, he would always say, "Well, I will take the appendix against the field." One always does have to consider the possibility of chronic appendiceal abscess, but I think we can rule it out on account of the duration of the story, the lack of emaciation, the lack of fever and the lack of the typical onset with the attack, and perhaps the presence of diarrhea.

Actinomycosis perhaps would come to mind from the presence of a mass, but again, if the story is as long as the protocol tells us, one would expect the patient to have a frank abscess by this time. Furthermore, in my experience, blood is not

a feature in dealing with actinomycosis of the cecum.

Sarcomatous lesions, of course, are more frequent in the small than in the large bowel, and the pressure defect is lateral in type, not the annular type that these x-ray films suggest. The patient could have had bleeding from ulceration, but he was in good physical condition, had a surprisingly good red-cell count, and his white-cell count was only slightly elevated. I think that we can rule out sarcomatous lesions, particularly the lymphoblastic group.

Occasionally one sees a rare case of simple ulceration of the colon. We have had two or three such cases in our clinic at the Beth Israel Hospital. They are generally seen in the older age group, patients who are around fifty or more, and are characterized by bleeding, and by the presence of an ulcer, generally of good size, picked up by x-ray examination. What the etiology is, I do not know. We have not seen them in the perforated stage. Here we find a definitely long, tubular, constricting lesion, so we can rule out simple ulceration of the colon.

Diverticulitis, of course, will cause a constriction and a mass. Diverticulitis is a disease of the old-age group. It is usually, however, not characterized by bleeding. It is almost invariably multiple, and it is much more prone to involve the left colon than the right. The chances are, from all these facts, that we can discard that as a possibility.

Ileocecal tuberculosis is a possibility. Here, in the East, where the majority of milk is pasteurized, the surgical tuberculous lesions of childhood are rare. They have disappeared remarkably in the last thirty years or so. Another large entity that was frequently placed in the group of ileocecal tuberculosis has been removed from that category by the recognition of regional enteritis, or terminal ileitis. Ileocecal tuberculosis, however, unquestionably occurs. Sometimes tubercle bacilli can be picked up in the stools. In the last case that I personally encountered, there was marked involvement of the appendix, which resembled a good-sized yellow banana. That patient had tubercle bacilli that were readily identified in the stool. Usually, of course, there are accompanying signs—evidence of calcareous nodes elsewhere in the abdomen or signs in the chest. It is frequently accompanied by quite severe bleeding and usually by tenesmus. This man was in good physical condition and had no anemia, and I should say that his general condition did not fit the picture of ileocecal tuberculosis.

The patient was twenty-three years old, and because of that, at first glance, one rules out cancer of the ascending colon. Of course that does not always hold. We have had four or five cases of intestinal neoplasm in the twenty-year-old group. One boy that we had a couple of years ago came in with a mass and had a distinct family history of carcinoma, and his father had died less than five years before of carcinoma of the rectum. He had car-

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

COBURN — Clarence O. Coburn, M.D., of Candia, died March 30. He was in his sixty-second year.

Dr. Coburn, son of William P. and Sarah (Hubbard) Coburn, was born in Manchester and graduated from Tufts College Medical School in 1906. He was vice-president of the Manchester Rotary Club, a trustee for several years of the Currier Gallery of Arts, president of the Medical Staff at the Elliott Hospital and a member of the Manchester, Hillsborough County and New Hampshire medical societies. He served as president of the New Hampshire Medical Society in 1939.

He is survived by his widow, two daughters, one son, four brothers and one sister.

NOTICES

JOSEPH H. PRATT
DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9-10 a.m.

MEDICAL CONFERENCE PROGRAM

Wednesday, May 3 — Harmful Effects of Recumbency in the Treatment of Heart Failure. Dr. Samuel Levine.

Friday, May 5 — Errors in Cardiovascular Diagnosis. Dr. Paul D. White.

Wednesday, May 10 — Electric Shock Treatment. Dr. Abraham Myerson.

Friday, May 12 — The Value of Nephrostomy. Dr. Roger Graves.

Wednesday, May 17 — Some Clinical Aspects of Coccidioidomycosis. Dr. Norman Culiner.

Friday, May 19 — Diagnosis of Pancreatic Disease. Dr. Joseph H. Pratt.

Wednesday, May 24 — Prefrontal Lobectomy Indications and Results. Dr. Kurt Goldstein.

Friday, May 26 — Clinicopathological Conference. Drs. David Ayman and H. E. MacMahon.

On Tuesday and Thursday mornings Dr. S. J. Thannhauser will give medical clinics on hospital cases.

On Monday mornings clinics will be given by Dr. Samuel Proger. On Saturday mornings clinics will be given by Dr. William Dameshek.

BOSTON CITY HOSPITAL ALUMNI
ASSOCIATION

There will be a clinical meeting of the Boston City Hospital Alumni Association on Saturday, May 6, in the Cheever Amphitheater, Dowling Building.

PROGRAM

Sternal Puncture Therapy. Dr. Henry Baker.

Treatment of Hydrocephalus in Cephalic Presentation (with motion pictures). Dr. Arthur J. Gorma.

Fluoroscopic Method of Nailing Hips and the Results (with motion pictures). Dr. Newton C. Browder.

Prevention and Treatment of Pulmonary Embolism (with lantern slides). Dr. Everett E. O'Neil.

Penicillin. Dr. Chester S. Keefer.

Luncheon for the alumni, as guests of the trustees, will be held in the House Officers' Dining Room at 12:30 o'clock.

WASHINGTONIAN HOSPITAL

Mr. Reuben L. Lurie, chairman of the Parole Board, Massachusetts Department of Correction, will give the final lecture in the series on alcoholism, being held under the cosponsorship of the Washingtonian Hospital and the Committee on Alcoholism of the Boston Council of Social Agencies on Friday evening, May 12, at 7:30, at Zero Marlborough Street, Boston. His topic will be "Alcoholism, Criminology and Parole." Mr. Elwood H. Hettrick, dean of the Boston University Law School and a member of the Board of Directors of the hospital will preside.

NEW ENGLAND HOSPITAL
FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, May 4, in the classroom of the Nurses' Residence at 7:15 p.m. Dr. Susannah Friedman will present and discuss the following two cases from the Urological Department: "Multiple Bilateral Renal and Ureteral Calculi and Their Removal" and "Bladder Papillomas — Late Complications."

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING
THURSDAY, MAY 4

THURSDAY, MAY 4

*9:00-10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

7:15 p.m. *New England Hospital for Women and Children*. Monthly clinical conference and meeting of the staff.

FRIDAY, MAY 5

*9:00-10:00 a.m. Errors in Cardiovascular Diagnosis. Dr. Paul D. White. Joseph H. Pratt Diagnostic Hospital.

*12:00 p.m. Massachusetts Central Health Council. The Pioneer, Y. W. C. A., 140 Clarendon Street, Boston.

SATURDAY, MAY 6

*9:00-10:00 a.m. Medical clinic. Dr. William Dameshek. Joseph H. Pratt Diagnostic Hospital.

12:30 p.m. Boston City Hospital Alumni Association. Cheever Amphitheater, Dowling Building.

*10:00-11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, MAY 8

*9:00-10:00 a.m. Medical clinic. Dr. Samuel Proger. Joseph H. Pratt Diagnostic Hospital.

*12:15-1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, MAY 9

*9:00-10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12:15-1:15 p.m. Clinicoröntgenological conference. Peter Bent Brigham Hospital.

WEDNESDAY, MAY 10

*9:00-10:00 a.m. Electric Shock Treatment. Dr. Abraham Myerson. Joseph H. Pratt Diagnostic Hospital. New England Oto-Laryngological Society. Spring meeting. Massachusetts Eye and Ear Infirmary.

*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

APRIL 29. Long Island College of Medicine. Page ix, issue of March 30.
MAY 3-26. Joseph H. Pratt Diagnostic Hospital. Medical Conference program. Notice elsewhere on this page.

MAY 8-14. War Conference on Industrial Medicine, Hygiene and Nursing. Page x, issue of March 23.

MAY 11. Problems of the Department of Industrial Accidents. Mrs. Emma S. Tausant. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

MAY 12. Washingtonian Hospital. Lecture on Alcoholism. Notice elsewhere on this page.

MAY 23 and 24. Massachusetts Medical Society. Annual meeting. Hotel Statler, Boston.

JUNE 7-13. American Board of Obstetrics and Gynecology. Page x, issue of March 23.

JUNE 8-10. American Board of Internal Medicine. Page x, issue of April 20.

JUNE 12-16. American Medical Association. Page 798, issue of November 18.

JUNE 12-16. American Physicians' Art Association. Page x, issue of March 2.

OCTOBER 3-5. American Public Health Association. Page ix, issue of March 30.

DISTRICT MEDICAL SOCIETIES

SUFFOLK

MAY 4. Censors' Meeting. Page xiii, issue of February 10.

WORCESTER

MAY 10. Annual meeting.

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ALLOXAN DIABETES WITH DIABETIC COMPLICATIONS*

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BOSTON

THE production of fatal hypoglycemia in rabbits by the intravenous administration of alloxan⁶ (the uride of mesoxalic acid) was described in 1937 by Jacobs.¹ Grossly, the organs of these rabbits appeared normal. No histologic studies were described. In 1943, Dunn, Sheehan and McLetchie² made similar physiologic observations and, in addition, pointed out that there was coincident selective necrosis of the islets of Langerhans without injury to the acinar tissue of the pancreas. Bailey and Bailey⁴ confirmed both the physiologic and the histologic findings of Jacobs and of Dunn, Sheehan and McLetchie. They further found with rabbits that if death in hypoglycemia is prevented by the administration of intravenous dextrose, permanent diabetes mellitus develops within twenty-four hours. Brunschwig, Allen, Goldner and Gomori⁵ demonstrated transitory hyperglycemia after the intravenous administration of alloxan in rabbits and produced sustained hyperglycemia in 5 dogs. Later Goldner and Gomori⁶ described in detail the production of alloxan diabetes in dogs. They also injected alloxan into 3 human patients with carcinomatosis. One of the carcinomas arose in the islets of Langerhans. They found no change either in the blood-sugar levels or in the clinical condition of any of the patients. In later papers, Dunn, Kirkpatrick, McLetchie and Telfer⁷ and Dunn and McLetchie⁸ discussed their experiments on rabbits in detail and recorded the production of sustained hyperglycemia in 5 of 8 albino rats injected with alloxan. A more complete summary of the literature appears in the recent progress article by Joslin,⁹ which, however, does not include a paper by Hard and Carr¹⁰ who report the effect on rabbits of doses of alloxan of various sizes.

The purpose of this paper is to describe the occurrence of diabetic cataracts in rabbits made permanently diabetic by the use of alloxan, to discuss the effect of repeated small doses of alloxan in rabbits, as well as the lesions in the islets of Langerhans of rabbits immediately after the production of alloxan diabetes, and to describe a simple method for the production of alloxan diabetes in the rat, with the development of cataracts in two animals and of diabetic coma in another.

DIABETIC CATARACTS IN RABBITS

Cataracts developed in 5 rabbits made diabetic by the intravenous administration of 200 mg. of alloxan per kilogram of body weight, as previously recorded.⁴ In each the cataract developed between four and six weeks after the diabetes was induced. All the rabbits had severe diabetes and were kept alive and in good condition from two and a half to five and a half months with the injection of 13.4 to 8 units of insulin daily.

The development of the cataracts has been followed by Dr. William Beetham, who reports that lens opacities are easily seen with oblique illumination and the ophthalmoscope. These changes are chiefly subcapsular, and are now more advanced in the posterior cortex, where they seem to appear earlier than in the anterior cortex. There is no definite arrangement of the opacities, although a rosette-shaped design in the posterior cortex has been noted in several animals and in some others the opacities are nearer the lens equator, forming a ring, with the pole of the lens relatively clear. Marked vacuole formation and irregular water clefts are seen with the ophthalmoscope. The slit-lamp (magnification 40x) also shows diffuse cloudiness of the cortical layers and, in a few rabbits, many highly refractile and iridescent crystals resembling the cholesterol crystals seen in human lenses were observed. The changes may progress rapidly, the fundus oculi being visible at one examination and invisible three weeks later. In the rabbit having diabetes for the longest period, five months, the

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cataracts have reached sufficient density to prevent visualization of the details of the fundus.

EFFECT OF REPEATED SMALL DOSES OF ALLOXAN IN RABBITS

Complete histologic studies made on several alloxan-diabetic rabbits revealed that the tissue changes related to the administration of alloxan were confined to necrosis of the islets of Langerhans, mild tubular degeneration of the kidneys and slight fatty metamorphosis of the liver. There were no morphologic changes in any of the endocrine glands other than in the islets of Langerhans. The histologic findings in alloxan diabetes offer further direct evidence that lesions of the islets of Langerhans are sufficient to produce the physiologic changes of diabetes mellitus. Thus, an experimental method is now available for the production of pancreatic diabetes without loss of the external secretion of the pancreas.

It seemed important to investigate the effects of repeated small injections of alloxan, to see whether these would have a cumulative effect and, if so, whether a permanent or a transient diabetes would result. To test these possibilities, 8 rabbits were given small repeated intravenous injections of alloxan.

Three rabbits were given 20 mg. of alloxan per kilogram of body weight intravenously three times a week for two months, and their blood sugars, twenty-four-hour urine samples and general condition were carefully followed. None developed hyperglycemia, glycosuria or any sign of diabetes.

Another 3 rabbits were given 40 mg. of alloxan per kilogram in repeated intravenous injections. Two of these had daily injections and developed diabetes after the seventh and thirteenth injections respectively. After two blood-sugar levels over 200 mg. per 100 cc. had been obtained, with concomitant glycosuria, both rabbits were sacrificed for pathological study. In the pancreases, there were striking changes in the islets of Langerhans. The cells of each islet showed a variety of lesions. Some cells, especially those at the periphery of the islets, appeared essentially normal. In other cells, the nuclei were well preserved, as was the ground substance of the cytoplasm, but the granules were not present. Numerous cells presented a clear-cut picture of hydropic degeneration, which has been shown to be a reversible change.¹¹⁻¹⁵ Among the cells with hydropic degeneration there were occasional ones with large, clear vacuoles but with the nuclei staining in a homogeneous manner and without chromatic pattern. This appears to be an irreversible change because of the nuclear damage. Mitoses were seen in several islet cells, but in no case was there more than one mitosis in an islet (Fig. 1). This complex picture of normal cells, slightly injured cells, cells with hydropic degeneration, irreversibly damaged cells and a mitosis in a

single islet is not clearly duplicated in any other form of experimental diabetes or in human patients. It seems best interpreted as a complex response to an injurious agent, with some cells capable of survival if the agent is removed, whereas others are dead and are being replaced by mitotic division of surviving islet cells.

In the third rabbit receiving 40 mg. of alloxan per kilogram three times a week, diabetes appeared after the tenth injection, with the blood-sugar level reaching 332 mg. On cessation of the injections, the diabetes seemed to disappear. Subsequent and careful observation over two and a half months, however, shows that mild diabetes persists, with occasional blood-sugar levels as high as 228 mg.

The seventh rabbit received successive doses of alloxan amounting to 20, 40, 60 and 60 mg. per kilogram, with two-day intervals between the first three injections and a ten-day interval between the third and fourth. Following the last injection, permanent severe diabetes appeared, with the blood-sugar level reaching 490 mg. and with 6.4 per cent glycosuria. This rabbit has remained diabetic for five and a half months and still requires $2\frac{1}{2}$ units of crystalline insulin daily.

The eighth rabbit received 20 mg. of alloxan per kilogram three times a week for seven, one-day intervals. After the fourth injection, hyperglycemia appeared for one day, with blood-sugar levels of 272 and 300 mg. Despite continued injections, the diabetes had disappeared by the next day and did not recur during the next two and a half months of careful observation. This transitory diabetes has not appeared in another animal, although in one, reported above, the diabetes became much milder after the injections were discontinued.

It appears that repeated doses of 20 mg. per kilogram were not sufficient for the production of diabetes. This was the case even though the total amount of alloxan injected was extremely large, one rabbit receiving a total of 580 mg. per kilogram. Doses of 40 mg. per kilogram, on the other hand, regularly produced diabetes in all rabbits in which they were tried. In these animals, a single dose had no effect, as shown by repeated determinations of the blood-sugar level on the day of injection. In those rabbits that developed diabetes, however, the morning blood-sugar level tended to rise a little each day until diabetes finally appeared.

These results suggest a cumulative effect of alloxan, and further indicate that repeated doses of 40 mg. per kilogram or larger are necessary to produce sufficient accumulation to influence the islets of Langerhans. The hydropic degeneration found immediately after the development of diabetes^{11, 12} suggests that, as pointed out by Allen,¹³ Lukens and Dohan,¹⁴ and Copp and Barclay,¹⁵ who studied other animals in experimental diabetes produced by partial depancreatotomy or by crude anterior-pituitary extracts, the injury in these particular cells is

reversible rather than permanent. Such changes have been reported in early cases of human diabetes.¹⁶⁻¹⁸

ALLOXAN DIABETES IN RATS

The effects of alloxan on rats have recently been studied. Fifteen rats were made diabetic in this way. The intraperitoneal and intravenous routes of administration did not prove satisfactory. Of 6 rats injected intraperitoneally with from 200 to 400 mg.

Diabetic cataracts developed in 2 rats made diabetic with alloxan and kept alive for four months. In one of these, cataracts have completely obstructed all vision.

Diabetic acidosis developed in 1 rat. This animal, which weighed 149 gm., received 200 mg. of alloxan per kilogram subcutaneously. Forty-eight hours later, marked polyuria and polydipsia were apparent and the blood-sugar level was 820 mg. The rat



FIGURE 1. An Island of Langerhans from the Pancreas of a Diabetic Rabbit.

This rabbit had been given seven intravenous injections of alloxan, each of 40 mg. per kilogram of body weight. Some of the cells are essentially normal; many show hydropic degeneration, a few are dead; and one is in mitosis. (Camera lucida drawing at $\times 1100$.)

of alloxan per kilogram, only 1 developed diabetes. Three died with extensive liver necroses, and 2 remained alive and well. Subcutaneous Nembutal was necessary to alleviate the pain, which lasted for several hours after this injection. At autopsy, considerable inflammatory reaction was found on the peritoneum. Four rats were injected intravenously with 150 to 300 mg. of alloxan per kilogram. All died within two days.

The subcutaneous route of administration was used in 26 rats, with dosages varying from 100 to 300 mg. per kilogram. Fourteen of these developed diabetes, 4 died, and 8 have continued alive and well. Two hundred milligrams of alloxan per kilogram proved to be the most feasible dose, since 12 of the 15 rats receiving this dose developed diabetes.

appeared sick. On the third day, acetone appeared in the urine and the animal lay on its side, apparently moribund. It received 0.2 units of insulin, which was repeated in two hours. Marked improvement supervened, and by the fifth day the animal appeared alert and well on a maintenance dose of 0.5 units of crystalline insulin daily. Observations on diabetic acidosis induced by alloxan in rabbits have already been reported from this laboratory.⁴

One rat also developed diabetic coma, which is a further indication that the diabetes induced by alloxan in rats is severer than that produced by pancreatectomy. This animal received 200 mg. of alloxan per kilogram subcutaneously. By the third day, polydipsia and polyuria were evident. On the fourth day the blood-sugar level was 720 mg., aceto-

nuria was marked, and the rat developed typical diabetic coma with extreme polydipsia, dry tongue, Kussmaul respiration and drowsiness, leading eventually to unconsciousness and death that evening.

The histologic findings in this case were of considerable interest. In the pancreas, the islets of Langerhans were destroyed. Except for one islet, there were no traces of islet cells of any type, and the original sites of the islets could be found only after search. The acini were essentially normal in appearance. In contrast to the findings in rabbits, but in conformity with those in other rats, there was a diffuse infiltration of the interstitial tissue with mononuclear cells and polymorphonuclear leukocytes. These were scattered uniformly throughout the stroma of the pancreas; no concentration was found about the ducts or in the sites formerly occupied by the islets of Langerhans. In the liver there was congestion of the sinusoids of the central portions of lobules. No necroses were present. Many of the liver-cord cells contained small fat droplets. One adrenal gland contained a small area of necrosis in the cortex, with infiltration by polymorphonuclear leukocytes. Similar lesions have been encountered in control rats, for which reason this finding is not regarded as significant. The other adrenal gland was normal. There was conspicuous tubular degeneration in the kidney. The proximal convoluted tubules were swollen, and small vacuoles were present in the basal portions of many cells. The epithelium of the distal convoluted tubules was shrunken in some places. These tubules and also the collecting tubules contained eosinophilic material, which appeared granular. No changes were noted in the interstitial tissue, and no polymorphonuclear leukocytes were seen. The blood vessels of the kidney, as well as those of other organs, were normal. The degree of renal damage was far greater than that in any of the rabbits examined. Study of other organs failed to reveal any deviations from the normal. All 6 rats studied histologically showed selective necrosis of the islets of Langerhans. Unlike the rabbits, however, the 5 rats that received the drug intraperitoneally or intravenously showed extensive necrosis of the liver and extremely severe lesions of the kidney, predominantly tubular in type. The rat described above that received alloxan subcutaneously and developed diabetic coma did not have liver necrosis.

It thus appears that diabetes may be produced by alloxan in rabbits with only slight injury to organs other than the islets of Langerhans. In rats, diabetes may be produced but with considerably greater in-

jury to other organs. When an appropriate dose is administered by the subcutaneous route, however, the changes in the majority of cases are not so severe as to cause death.

SUMMARY

Bilateral diabetic cataracts developed in four to six weeks in rabbits made diabetic with alloxan.

The production of alloxan diabetes in rabbits depends on the dosage. Repeated injections of 20 mg. per kilogram were not sufficient to produce diabetes. Forty-milligram doses produced diabetes within two weeks in 2 rabbits, suggesting a cumulative effect of alloxan with the larger dose.

Histologic studies of the pancreas in 2 rabbits immediately after the production of diabetes by the repeated injection of 40 mg. of alloxan per kilogram revealed that some cells of the islets of Langerhans showed hydropic degeneration, others showed irreversible changes, and some were essentially normal, whereas occasional cells were in the process of mitotic division. The pancreatic acini were normal.

In rats, the subcutaneous administration of 200 mg. of alloxan per kilogram is feasible for producing diabetes.

The occurrence of cataracts and of diabetic acidosis and coma in the rat is reported.

Mrs. Leech and Miss Hazel Hunt supervised the chemical analyses made in this study. They and Miss Barbara Jacob gave valuable technical assistance.

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INFECTIONS ASSOCIATED WITH AN EPIDEMIC OF PRIMARY INTERSTITIAL PNEUMONIA*

CUTTING B. FAVOUR, M.D.†

BOSTON

IN 1935, Bowen¹ reported the occurrence of pneumonia in 5 to 25 per cent of cases of so-called "flu" in which routine roentgenograms of the chest were taken. Since that report, clinical attention has been focused particularly on cases of respiratory infection with roentgenologic evidence of primary interstitial pneumonia; little information has been accumulated regarding the minor related respiratory infections. In 1940, however, Reimann and Havens² reopened the latter phase of the subject with the report of an epidemic in which 88 per cent of the patients were ill with nasopharyngolaryngitis, 6 per cent had in addition tracheobronchitis and 6 per cent had tracheobronchopneumonia. Dyer and his co-workers³ did not find so great an association of minor illness with an outbreak of Q fever. Dingle and others⁴ observed a large number of cases of minor respiratory infections that occurred at the same time as an outbreak of primary interstitial pneumonia at Camp Clairborne, Louisiana, but could find no direct epidemiologic relation between the two groups of cases. Iverson,⁵ reporting an epidemic in a boys' camp, stated that 60 to 80 per cent of approximately 100 persons had respiratory symptoms, 35 per cent were confined to bed with a severe cough and only 6 per cent suffered from primary interstitial pneumonia.

From June, 1942, to February, 1943, inclusive, an intramural epidemic of atypical pneumonia and related respiratory illness occurred among the personnel, numbering approximately 300, of the Peter Bent Brigham Hospital. This afforded an excellent opportunity to study the relation between common upper respiratory infections and the current form of atypical pneumonia. A description of this epidemic and an analysis of its salient features follow.

CLINICAL DATA

First Local Epidemic

On June 13, 1942, Dr. A₁ developed cough, malaise and fever ranging up to 104°F. On June 14, a roentgenogram of the chest showed an extensive pneumonia. Instead of going to bed, he remained ambulatory in order to attend examinations that took place on June 15, 16 and 17. For the next three weeks he was desperately sick. Violent nonproductive paroxysms of coughing, cyanosis, periodic delirium and bilateral pulmonary mottling (similar

to that of terminal miliary tuberculosis) as shown by x-ray examination characterized his illness. Recovery was delayed for three months.

Between examinations Dr. A₁ talked outdoors to Drs. B₁, B₂ and B₃, with whom he also rode about in a car. He spent his evenings and nights at home during this period, thus exposing his wife, B₄. B₁ returned to the Brigham Surgical Service, where he worked until admitted as a patient on July 4, seventeen days following his first exposure to A₁, with a severe atypical pneumonia. B₂ returned to the Massachusetts General Hospital Surgical Service, where he too worked until hospitalized on July 4, seventeen days following his first exposure to A₁, with an even more persistent atypical pneumonia. B₃ left for a new position on the medical service of another hospital, where he developed a less acute but equally persistent atypical pneumonia on July 5, eighteen days following his first exposure to A₁. Also on July 5, B₄, eighteen days following her first exposure to A₁, developed severe atypical pneumonia (Table 1).

B₁, who came to the Peter Bent Brigham Hospital, developed his illness in two stages: a prodromal period of five days marked by chilly sensations, low-

TABLE 1. Incubation Periods in First Local Epidemic.

SUBJECT	INCUBATION PERIOD	
	days	
B ₁ .. .	15	17
B ₂ .. .	15	17
B ₃ .. .	16	18
B ₄ .. .	15	18

grade fever, muscle aches and a slight, dry cough; and an acute stage of ten days characterized by high fever (103 to 104°F.), a paroxysmal dry cough, cyanosis, scattered bronchiolar rales and, as shown by roentgenographic examination, a diffuse mottling of the left lower lobe.

Three student nurses (C₁, C₂ and C₃) and 1 graduate nurse (C₄) who worked with B₁ during his prodromal period became ill, as shown in Table 2. In contrast to C₁, C₂ and C₃, whose oral temperatures did not rise above 100°F., C₄ had fever up to 102°F., the classic cough of atypical pneumonia and increased hilar markings on the left side as shown by x-ray. Two of the nurses (C₁ and C₂) had gastrointestinal upsets.

During the acute stage, B₁ was carefully isolated in a single room on a third-floor ward.† Three stu-

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‡The Peter Bent Brigham Hospital is built on the pavilion plan. The wards are on the first, second and third floors of five isolated buildings. Single third floor rooms in four buildings and single rooms on the wards proper were used for individual isolation.

dent nurses (C₅, C₆ and C₇) who took care of him became ill, as shown in Table 3.

The gastrointestinal upsets in the two pairs of contacts, C₁ and C₂ and C₅ and C₆, were unusual in that they did not occur in each pair on the same day, were accompanied by tracheobronchitis or prostration out of proportion to the disturbance in the fluid balance and did not yield enteric pathogens in the cultures of the stools.

The sick nurses were isolated in their rooms in the nurses' home and the single rooms of a previously

A complete list of the hospital personnel who were exposed to him is given in Table 4. Of 10 direct contacts, 7 became sick after a delay of one to fourteen days. The illnesses included 2 cases of pneumonia, 3 of tracheobronchitis and 2 of so-called "colds." The probable incubation period was seven to fourteen days.

X₃, a houseofficer who developed atypical pneumonia, was isolated on a third-floor single-room ward. A strict isolation technic was observed, with the use of masks, gowns and scrubbing. Contacts

TABLE 2. *Contacts of B₁ During Prodromal Period.*

SUBJECT	POSITION	DEGREE OF CONTACT	INCUBATION PERIOD days	ILLNESS	DURATION OF ILLNESS days
C ₁	Student nurse	Close	6-11	Gastrointestinal upset with moderate tracheobronchitis	1
C ₂	Student nurse	Close	10-17	Gastrointestinal upset with moderate tracheobronchitis	2
C ₃	Student nurse	Moderately close	10-16	Tracheobronchitis with fuzzy hili and backache	14
C ₄	Graduate nurse	Close	7-13	Slight pneumonia	7

TABLE 3. *Contacts of B₁ During Acute Illness.*

SUBJECT	POSITION	DEGREE OF CONTACT	INCUBATION PERIOD days	ILLNESS	DURATION OF ILLNESS days
C ₅	Student nurse	Moderately close	1-11	Gastrointestinal upset with fatigue	1
C ₆	Student nurse	Moderately close	1-14	Gastrointestinal upset with fatigue	2
C ₇	Student nurse	Slight	6-12	Tracheobronchitis	3

TABLE 4. *Contacts of W₁ During Acute Illness.*

SUBJECT	POSITION	DEGREE OF CONTACT	INCUBATION PERIOD days	ILLNESS	DURATION OF ILLNESS days
X ₁	Visiting physician	Close	None
X ₂	Houseofficer	Close	1-12	Acute tracheobronchitis	13
X ₃	Houseofficer	Close	1-12	Atypical pneumonia	7
X ₄	Head nurse	Minimal	1-9	Slight tracheobronchitis	1
X ₅	Student nurse	Moderately close	None
X ₆	Student nurse	Moderately close	1-9	Head cold	2
X ₇	Graduate nurse	Moderately close	1-14	Severe cold	2
X ₈	Student nurse	Moderately close	?	Tracheobronchitis with backache	?
X ₉	Student nurse	Moderately close	1-13	Atypical pneumonia	6
X ₁₀	Kitchen maid	Indirect	7-20	Tracheobronchitis	4
X ₁₁	Kitchen maid	Indirect	None
X ₁₂	Orderly	Slight	None

unexposed medical ward. One cross infection seemed to come from the C group, occurring in D₁, a graduate nurse, who developed moderately severe tracheobronchitis lasting a week twelve days after close contact with her roommate, one of the above group.

Second Local Epidemic

During the first two weeks of August, 1942, a lull in respiratory infections among the hospital personnel occurred, amounting in effect to a natural quarantine period. On August 12, W₁ was admitted to the private pavilion on the eleventh day of a moderately severe atypical pneumonia. Up to three days before his discharge from the hospital on August 24, he had fever and a paroxysmal dry cough.

during the prodromal period before isolation and later during the acute illness are listed in Tables 5 and 6. Of the 15 contacts during the prodromal period, 4 became ill — 3 with tracheobronchitis and 1 with an acute gastrointestinal upset. Of the 12 contacts during the period of acute illness, 7 became ill — 5 with tracheobronchitis (including 3 with an additional gastrointestinal upset), 1 with pneumonia and 1 with a "cold." The probable incubation periods varied from nine to thirteen days. X₈, a student nurse who developed atypical pneumonia, did not have a prodromal period but became sick abruptly and was isolated in another part of the hospital. Table 7 shows the contacts. Of the 8 contacts, 6 became ill — 3 with tracheobronchitis, 2 with pneumonia and 1 with an acute gastrointestinal up-

set. Both contacts who remained well had been previously exposed to cases of atypical pneumonia.

The proportion of student nurses who became ill as a result of exposure to atypical pneumonia was greater than it was among graduate nurses. In general, visiting physicians, houseofficers and nurses who had been repeatedly exposed to atypical

until November 14. This group survey brought to our attention all persons with fever and most of those with symptoms. On September 28, a sixteen-bed medical ward was set aside for so-called "virus patients." Five days later a thirty-bed ward was substituted for this purpose. There for the next month the daily census of epidemic patients — those with

TABLE 5. *Contacts of X₁ During Prodromal Period.*

SUBJECT	POSITION	EXPOSED TO PREVIOUS EPIDEMIC	DEGREE OF CONTACT	INCUBATION PERIOD days	ILLNESS	DURATION OF ILLNESS days
Y ₁	Head nurse	Yes	Minimal		None
Y ₂	Graduate nurse	Yes	Minimal		None	
Y ₃	Student nurse	No	Moderately close	9 11	Severe tracheobronchitis	14
Y ₄	Student nurse	No	Minimal		None	
Y ₅	Student nurse	No	Minimal		None	
Y ₆	Student nurse	No	Minimal		None	
Y ₇	Student nurse	No	Minimal		None	
Y ₈	Student nurse	No	Minimal	13 15	Tracheobronchitis	12
Y ₉	Student nurse	No	Minimal		None	
Y ₁₀	Student nurse	No	Minimal		None	
Y ₁₁	Student nurse	No	Minimal	1-11	Tracheobronchitis	2
Y ₁₂	Student nurse	No	Minimal	1-11	Gastrointestinal upset	1
Y ₁₃	Student nurse	No	Minimal		None	
Y ₁₄	Student nurse	No	Minimal		None	
Y ₁₅	Houseofficer	Yes	Close		None	

*Left hospital; no follow-up

TABLE 6. *Contacts of X₂ During Acute Illness*

SUBJECT	POSITION	EXPOSED TO PREVIOUS EPIDEMIC	DEGREE OF CONTACT	INCUBATION PERIOD days	ILLNESS	DURATION OF ILLNESS days
Y ₁₆	Graduate nurse	No	Close	1-13	Tracheobronchitis	7
Y ₁₇	Student nurse	No	Close	1-15	Tracheobronchitis and gastrointestinal upset	6
Y ₁₈	Student nurse	No	Minimal	1-12	Tracheobronchitis and gastrointestinal upset	10
Y ₁₉	Student nurse	No	Close	1-12	Tracheobronchitis	13
Y ₂₀	Student nurse	No	Indirect	5 13	Tracheobronchitis and gastrointestinal upset	11
Y ₂₁	Student nurse	No	Minimal		None	
Y ₂₂	Student nurse	No	Minimal		None	
Y ₂₃	Graduate nurse	No	Moderately close	1 8	Cold	2
Y ₂₄	Student nurse	No	Moderately close		None	
Y ₂₅	Houseofficer	No	Moderately close	10 12	Pneumonia	16
Y ₂₆	Houseofficer	Yes	Close		None	
Y ₂₇	Houseofficer	No	Close		None	

TABLE 7. *Contacts of X₃ During Acute Illness.*

SUBJECT	POSITION	EXPOSED TO PREVIOUS EPIDEMIC	DEGREE OF CONTACT	INCUBATION PERIOD days	ILLNESS	DURATION OF ILLNESS days
Y ₂₈	Head nurse	No	Moderately close	2-7	Gastrointestinal upset	2
Y ₂₉	Student nurse	No	Close	1-13	Pneumonia	5
Y ₃₀	Student nurse	No	Close	10 16	Tracheobronchitis	10
Y ₃₁	Student nurse	No	Close (1 day)	16	Tracheobronchitis	2
Y ₃₂	Student nurse	No	Minimal	11-13	Pneumonia	6
Y ₃₃	Student nurse	No	Minimal	11 12	Tracheobronchitis	4
Y ₃₄	Houseofficer	Yes	Close		None	
Y ₃₅	Houseofficer	Yes	Close		None	

pneumonia during previous years seemed to be relatively immune to the infection.

Major Epidemic

By September the number of cross infections was becoming too great to follow and isolate individually (Fig. 1). On September 21, the daily taking of temperatures (at 4 p.m.) of all persons working with patients was begun. This regimen was continued

pneumonia, tracheobronchitis, fever of unknown origin and fatigue — was never less than 20.

EPIDEMIC CONSIDERATIONS

During the nine months of this intramural epidemic, there occurred among approximately 300 hospital personnel who had direct contact with patients 231 cases of epidemically related infections (including 29 cases of primary interstitial pneumonia)

and 156 additional illnesses, not related to the epidemic, which were carefully studied for control purposes. These control illnesses are shown in Table 8 and Figure 1.

The epidemic cases occurred in four forms: atypical (primary interstitial) pneumonia, tracheobron-

chitis in 13 of the 60 doctors on the house staff — 7 physicians, 5 surgeons and 1 radiologist; in 13 of approximately 175 nurses residing in the hospital; in 2 orderlies who pushed atypical pneumonia patients to the X-ray Department; and in 1 x-ray technician who took films. The highest attack rate was in the

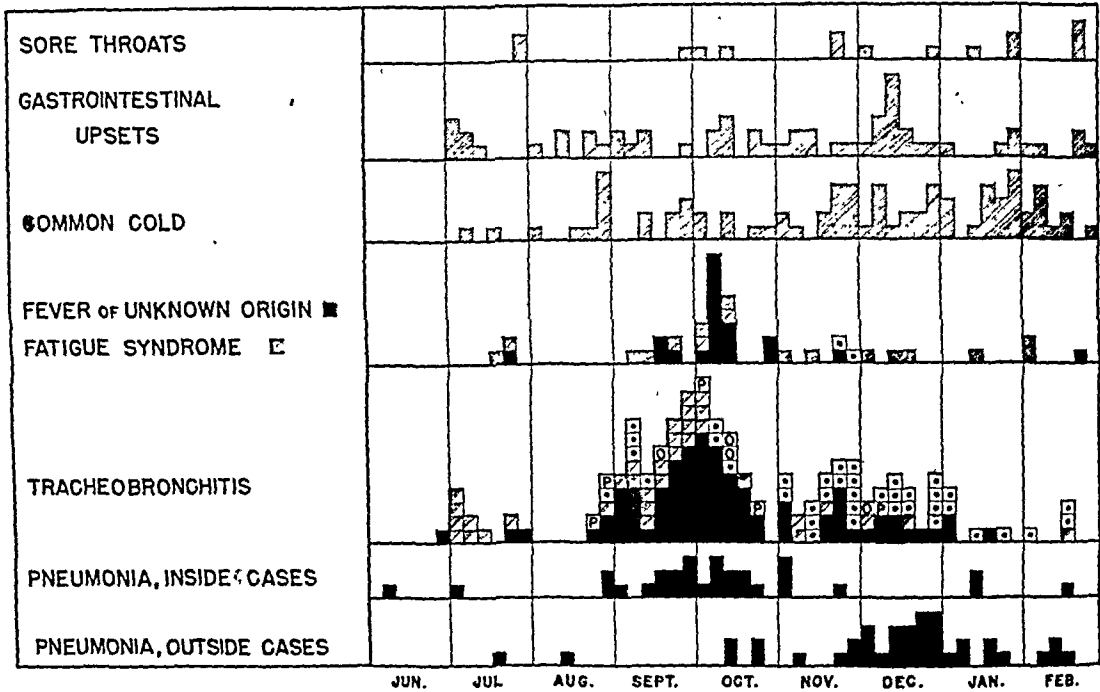


FIGURE 1. Occurrence of Known Disease in 300 Members of the Personnel of the Peter Bent Brigham Hospital (June, 1942, to March, 1943).

One square on the abscissa represents five days. One square on the ordinate represents 1 case whose day of acute onset fell within that five-day period. Of the cases of tracheobronchitis, the solid black squares are single attacks, the diagonal squares are first attacks, the spotted squares are second attacks (an asymptomatic interval of three or more weeks), the P squares are attacks of tracheobronchitis three or more weeks after recovery from atypical pneumonia, and the O squares vice versa. The black, diagonal and spotted squares apply similarly to fevers of unknown origin. Fatigue syndromes are gray only. It is to be noted that the majority of single and first attacks of tracheobronchitis came during the hospital epidemic of atypical pneumonia. On the other hand, the majority of repeat attacks came during the influx of outside cases of atypical pneumonia. The minor illnesses charted at the top apparently did not bear on the epidemic syndromes.

chitis, a fatigue syndrome and fever of unknown origin.

Atypical pneumonia. Among the approximately 300 hospital personnel, 29 persons contracted atypical pneumonia. This was 43 per cent of the total

X-ray Department where 4 of the 9 members, comprising physicians, nurses and technicians, contracted the disease. In addition, the valet of a private patient developed atypical pneumonia thirteen days after a one-day exposure on the virus ward.

Tracheobronchitis. This was the most frequent form of epidemic infection; 164 attacks, or 71 per cent of the 231 epidemic infections, occurred in 111 persons. Seventy were single attacks and 22 were first attacks. Of the former, 4 were followed after three weeks or more of normal health by atypical pneumonia, 1 occurred two months after recovery from atypical pneumonia, and 1 was the first of two widely separated attacks that occurred three months after atypical pneumonia. Most interesting were 11 first attacks that became chronic with repeated exacerbations on re-exposure to virus patients. An example of these is a student nurse who was sent home to convalesce when a period of two weeks off

TABLE 8. Incidence of Unrelated Illnesses.

DIAGNOSIS	NO. OF CASES
Sore throat.....	15
Gastrointestinal upset.....	56
Common cold.....	76
Infectious mononucleosis.....	3
German measles.....	3
Measles.....	1
Active tuberculosis.....	2
Total.....	156

cases of atypical pneumonia seen in the hospital during the nine months of intensive study. The attack rate was highest among those most directly in contact with other cases of pneumonia and in those most overworked. Atypical pneumonia developed

duty had proved ineffectual in alleviating her symptoms. Ten days later her father developed pneumonia, which did not respond to a sulfonamide in the local hospital. On returning to work, the nurse continued to cough in characteristic paroxysms. Several periods of one or more weeks of bed rest did not clear the cough or the malaise and fatigability. On two occasions exposure to a patient with acute atypical pneumonia resulted in a return of symptoms. Roentgenograms of the chest and blood studies were repeatedly negative. The cough persisted through the first nine months and over a year later still recurred.

Of the patients with nonchronic tracheobronchitis who had more than one attack, 22 had two attacks and 6 had more than three, all separated by three or more weeks without symptoms. Characteristically, those who suffered multiple attacks had them when most heavily exposed to patients with atypical pneumonia or tracheobronchitis (Fig. 1). In some of those infected for the second time, the specific contact was known and the incubation period was found to be the usual seven to fourteen days.

Other epidemic syndromes. During the epidemic, a fatigue syndrome was observed in 15 patients (Fig. 1). Fever of unknown origin (21 patients with twenty-three attacks), consisting of a low-grade oral temperature of not over 100°F., accompanied the fatigue syndrome during the mass temperature-taking. Occasionally there was a one-day to three-day rise of temperature to 102°F. or more, with acute prostration but without localizing physical signs or abnormal laboratory findings. It was interesting that none of the patients with either of these syndromes contracted cross infections from patients with tracheobronchitis or atypical pneumonia when out on the virus ward for study.

DISCUSSION

The relation between nonpneumonic forms of epidemic or sporadic respiratory infections and atypical pneumonia is the subject of this report. Atypical pneumonia is usually thought of as a nonfatal, relatively noninfectious sporadic infection.⁷⁻¹¹ That may occur in epidemics.^{1, 3-5, 12, 14-16} In isolated cases, viruses have been implicated as the etiologic agent, with hens,¹⁸ cats¹⁹ and birds¹⁷ the vectors. Occasionally experimental animals have been infected with human material.¹⁸⁻²⁰ Recently, Rose²¹ succeeded in transmitting the disease from patients to young guinea pigs. In other hands the average patient yields no virus and gives no clues regarding where he acquired his illness. For this reason diagnostic criteria have been limited to the actual x-ray demonstration of a pulmonary lesion, the failure of the infection to respond to a sulfonamide, negative bacteriologic studies and eventual recovery.

In the group study at Camp Clairborne, Louisiana, conducted by Dingle and his co-workers,⁴ emphasis

was placed on related nonpneumonic respiratory infections. These workers found that tonsillitis could be separately classified, both symptomatically and by physical signs. A large group of other infections, however, called "bronchitis resembling atypical pneumonia" and "other diseases of the respiratory tract," could be differentiated from atypical pneumonia only by a milder course and by lack of x-ray evidence of pneumonia. Although a common etiologic agent seemed probable, specific epidemiologic or laboratory evidence of cross infection was not found.

In the present study, an epidemiologic relation between atypical pneumonia and related infections was present. On the other hand, the minor illnesses of all the institutional groups comprising sore throats, gastrointestinal upsets and common colds, did not seem to be related to the epidemic, although gastrointestinal symptoms were associated with cough in a few cases in which exposure to patients with atypical pneumonia about two weeks previously strongly suggested that they were suffering from the same infection. The total infections, including both epidemic and minor illnesses, comprised 387 attacks of illness in a population of about 300 people: Two hundred and thirty-one of these attacks (60 per cent) consisted of one or another of the epidemic syndromes. Of the epidemic cases, 12 per cent were atypical pneumonia, 16 per cent were fatigue or fever of unknown origin and 71 per cent were tracheobronchitis. If a person contracted a clinical epidemic infection, he had one chance in eight of having pneumonia, one in six of having fatigue or fever only and three in four of having tracheobronchitis. If a person previously unexposed had had no one of these syndromes, he was extremely likely to be infected as shown by the occurrence of 231 attacks of epidemic illness among approximately 300 people. It is also interesting that a chronic form of tracheobronchitis sometimes occurred.

SUMMARY

Two hundred and thirty-one epidemically related attacks of infection occurring among the personnel of the Peter Bent Brigham Hospital, numbering approximately 300, are reported. Twenty-nine persons had atypical pneumonia, 111 had 164 attacks of tracheobronchitis, 23 had fever of unknown origin and 15 had a fatigue syndrome. One hundred and fifty-six colds, sore throats, gastrointestinal upsets and other infections that occurred during the nine months of the study showed no correlation with the epidemic, although a few patients with atypical pneumonia and tracheobronchitis had gastrointestinal symptoms.

Cases of atypical pneumonia represented 12 per cent and those of tracheobronchitis 71 per cent of the epidemic syndromes.

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MEDICAL PROGRESS

HEMATOLOGY (Concluded)

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HEMORRHAGIC DISEASES

IN GENERAL one may say that there are three mechanisms concerned in the clotting of blood: the blood platelets, the capillary endothelium and certain enzymatic and chemical factors within the blood. A hemorrhagic condition may ensue if any of these mechanisms becomes impaired. Thus, one may classify the hemorrhagic diseases as follows: those concerned with an abnormality of the platelets, those with an abnormality of the capillary wall and those with an abnormality of the circulating clotting factors.

Platelet Abnormalities

The most frequent abnormality of platelets resulting in hemorrhage is great diminution in number. Some authorities claim that petechiae do not develop even in gross platelet deficiency unless the capillaries are simultaneously involved. Although it is true that patients with similarly reduced platelet counts differ in their hemorrhagic tendency, it cannot be denied that it is the low platelet count that initiates the bleeding; furthermore, a capillary defect in acute leukemia, aplastic anemia and so forth has not been established. The so-called "capillary defect" in idiopathic thrombopenic purpura may be more fanciful than real. Platelet diminution occurs when the bone marrow is seriously involved, as in chemical poisonings, leukemias and neoplasms and in severe deficiency states, — when the spleen is enlarged, and idiopathically, — perhaps owing to some unknown splenic mechanism, as in idiopathic thrombopenic purpura. That the sulfonamide drugs

occasionally result in thrombopenic purpura is reported by Gorham, Propp, Schwind and Climenko.⁴² These authors stress the close chemical relations between benzol, aniline, sulfanilamide and the other sulfonamide drugs and their often similar effects on the bone marrow. Of 8 patients developing thrombopenic purpura, 4 died. It is recommended that blood smears be routinely examined for a possible decrease in platelets during sulfonamide administration. Kracke and Townsend,⁴³ reporting 2 cases of thrombopenic purpura developing during sulfathiazole administration, further studied 23 patients under treatment with the drug. There was a possible slight reduction in platelet count on the third day of treatment, followed by a rather marked rise when the drug was discontinued. This may indicate a more frequent effect on the platelet precursors in the marrow than is customarily believed. The most likely mechanism however, is a hypersensitivity on the part of the bone marrow to the sulfonamides. This was demonstrated by Hurd and Jacox⁴⁴ in a patient who was found to be sensitive to both sulfathiazole and sulfadiazine following recovery from a severe thrombopenia that developed with sulfathiazole administration.

The occurrence of mild thrombopenic purpura during infectious states is not at all uncommon, particularly when there is splenomegaly — as in typhoid fever and malaria. In infectious mononucleosis, the platelets are characteristically normal in number to find a low platelet count in conjunction with abnormal lymphocytosis is ordinarily tantamount to making a diagnosis of acute leukemia. Rarely, however, thrombopenic purpura and infectious mononucleosis coexist. Tager and Klinghoffer⁴⁵ report

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case of an infectious disease characterized by abnormal lymphocytosis and extreme thrombopenia, which suggested acute leukemia to most observers. Since, however, anemia was not present and the lymphocytes were extremely variable in size and shape, infectious mononucleosis was considered possible and this disease — or a similar one — proved to be present. Lymphocytosis and thrombopenic purpura not uncommonly go together, as noted some years ago by Minot.⁴⁶ I have found this abnormality in a number of cases of the idiopathic type of thrombopenic purpura, often in association with leukopenia, suggesting a possible splenic reaction on the bone marrow.

The spleen and the marrow are probably closely related, most likely by way of certain hormonal mechanisms. When the spleen becomes enlarged, as in cirrhosis of the liver, splenic vein thrombosis and Gaucher's disease, leukopenia and thrombopenia are frequently found. Although the blood in these cases shows diminished leukocytes and platelets, the marrow shows hyperplasia of both leukocytic and megakaryocytic elements. In idiopathic thrombopenic purpura, the marrow is crowded with megakaryocytes, although the blood may be completely devoid of their end products, the platelets. The striking effect of splenectomy may indicate that the fundamental abnormality of this disease is a disturbed function of the spleen, which can be cured only by removal of the offending organ. Occasionally, thrombopenic purpura complicates pregnancy; this may present a very difficult therapeutic problem. Palliation by transfusions may tide the patient over until platelets begin to be made spontaneously; some cases, however, fail to respond and splenectomy must be seriously considered, else the patient may die of hemorrhage. In a case reported by Urbanski and Hutner,⁴⁷ the patient was delivered despite the purpura, but nineteen days later there was severe bleeding from the uterus, controlled only when splenectomy was performed. At birth, the infant had a transient thrombopenic purpura, which lasted a few days. Subsequent to splenectomy, the mother had three normal full-term pregnancies in which the children were free of purpura. However, in a case reported by Whitney and Barritt⁴⁸ in which splenectomy for thrombopenic purpura was performed at the age of fourteen, two pregnancies terminated in the delivery of thrombopenic babies, both of whom died of hemorrhagic disease. It is to be noted that the mother in this case continued, despite her splenectomy, to have active thrombopenic purpura, as evidenced by a low platelet count, a prolonged bleeding time and a greatly diminished clot retraction; this is quite in contrast with the usually good results of splenectomy. It is evident that the same deleterious influence that results in thrombopenia of the mother may act on the bone marrow of the developing fetus, producing thrombopenic purpura.

Abnormalities of Capillary Walls

Abnormalities of the capillary wall may be caused by many diverse conditions, such as ascorbic acid deficiency, infections involving the capillaries directly, — subacute bacterial endocarditis, meningitis and so forth, — toxins — as in certain infectious states and in uremia — and more or less vague conditions of increased capillary permeability. The end result of the capillary abnormality is bleeding into the skin or mucous membranes (or internally in the various organs). Davis⁴⁹ classified 500 cases of purpura of the skin; 37 per cent — comprising so-called "purpura simplex," Schonlein-Henoch purpura, pseudohemophilia and so forth — were idiopathic. The remainder of the cases were symptomatic: that is, secondary to chemical, bacterial, infectious and other states. In any one patient, multiple factors may contribute to the purpura: arthritis, the menopause and other endocrine factors, infection, edema and orthostasis.

Davis⁵⁰ uses the term "purpura simplex" for those cases showing spontaneous ecchymoses of the skin in the absence of demonstrable hematologic abnormalities. These cases are usually present in women who complain of easy bruising and the appearance of ecchymoses without trauma. They have been called "devil's pinches," "dead man's nips" and "dead man's pinch." Davis has found in these cases not only a strong hereditary tendency but also a high incidence of rheumatic fever, rheumatoid arthritis or some other form of arthritis. The platelet count, coagulation time, bleeding time, prothrombin time and clot retraction are all normal, but the tourniquet and intradermal snake-venom tests are usually positive. Treatment with various endocrine products, vitamins C and P, snake venoms and so forth, has been used, but is of questionable value. Since the condition is ordinarily of little significance, reassurance is probably the best form of therapy.

A condition that has recently assumed increasing importance is that of pseudohemophilia (von Willebrand's disease, Glantzmann's disease, hereditary hemorrhagic thrombasthenia or athrombocytopenic purpura). In his book on the hemorrhagic disorders, Quick⁵¹ gives an excellent description of the condition, with tables differentiating it from other hemorrhagic conditions. This disorder, although by no means clear cut, is nevertheless of great importance to those who have it, since they bleed excessively from small operative wounds such as those caused by dental extractions and hemorrhoidectomy. Cronkite and Lozner⁵² make this point with reference to military medicine, and show how a great deal of bleeding from small trauma may occur without too much in the way of laboratory abnormalities, except a slight and variable increase in the bleeding time. In some cases, the hemorrhagic tendency is extremely severe and even hemarthroses, similar to

those seen in hemophilia, may occur. The history of a hereditary bleeding tendency, which is not sex linked, can be obtained in some cases. The chief recognizable abnormality is a definitely prolonged bleeding time in the presence of normal blood-platelet counts, normal clot retraction, normal coagulation time, normal prothrombin time and a normal tourniquet test. The bleeding time in the same patient at different times, by different technics and in different parts of the body is highly variable. Thus, one of my patients had a bleeding time of two and a half hours in one ear, twenty minutes in the other and a few minutes in a finger. In the ear that had bled for two and a half hours, the bleeding time some weeks later was only three minutes. An abnormality in capillaries and in capillary retractility has been postulated, principally by Macfarlane,⁵³ chiefly on the basis of studies of the capillaries at the nail bed and their response to trauma. Macfarlane found that the capillaries in this condition were of distorted and often bizarre forms and showed no tendency to contract after injury. In my own cases, however, no such capillary abnormality was demonstrable; furthermore, distorted and bizarre capillary loops without demonstrable hemorrhagic tendency are frequent in vasomotor conditions and certain psychoses. In a recently described case of idiopathic hypoprothrombinemia,⁶⁴ a bleeding abnormality similar to that of pseudohemophilia was found, and the author makes the point that the abnormal coagulation mechanisms in the latter disease are by no means worked out. With this I heartily agree.

Abnormalities in Circulating Coagulation Factors

Abnormalities in the circulating coagulation factors comprise hemophilia, hypoprothrombinemia, such rare conditions as fibrinopenia and those associated with the presence in the blood of a circulating antithrombic constituent.

Hemophilia. The etiology of the sex-linked hereditary hemorrhagic disorder known as hemophilia remains as obscure as ever. Is it a defect in thromboplastin, in a portion of the globulin fraction of the serum or, as Tocantins⁵⁵ has recently observed, an excess in circulating antithromboplastin? Howell,⁵⁶ Quick,⁵⁷ Ferguson^{57, 58} and many others believe that there is a defect in the liberation of thromboplastin from peculiarly resistant platelets. On the other hand, the group at the Thorndike Memorial Laboratory in Boston has presented apparently convincing evidence that platelet-free plasma and a euglobulin fraction of the plasma are effective in reducing the coagulation time in hemophilia.⁵⁹ It is possible that these seemingly divergent views are fundamentally related. Thus, in a more recent report from the Thorndike Memorial Laboratory by Tagnon, Davidson and Taylor,⁶⁰ there is described a proteolytic enzyme resembling trypsin in the plasma that is found to be reduced in preparations of hemophilic

plasma. In this paper, "globulin substance" is criticized as being far from a pure material. It should be noted that this concept is closely similar to that of Ferguson, who for several years has maintained that hemophilia is due to a deficiency in serum tryptase. A wholly new concept is that of Tocantins,⁵⁵ who claims that hemophilic plasma has an activity against certain thromboplastin solutions five to eight times as great as that of normal plasma. He concludes that an excess of antithromboplastin is probably the primary cause of the delay in the inception of clotting of hemophilic blood. Tocantins's conclusions are based on the collection of plasma under special precautions and its effect on the clot-accelerating action of certain aqueous extracts of brain tissue. His experiments must await confirmation before their relation to hemophilia can be completely ascertained. Another new concept regarding the etiology of hemophilia is supplied by Pennell,⁶¹ who claims that the coagulation of blood is dependent on a sudden and massive disintegration of platelets, that this occurs only when the platelets and red-cell surfaces are in contact (conjugation), that in hemophilia the phenomenon of red-cell-platelet conjugation is reduced, and finally that "the hemophilic's red cells may be responsible for the diminished red-cell-platelet conjugation in this disease." It cannot be denied that this is an ingenious theory, but it too requires a good deal of confirmatory evidence before it can be accepted.

The treatment of hemophilia also remains as difficult as ever, although the control of external local bleeding by means of thrombin preparations has proved successful in many cases, particularly in dental extractions. The original thrombin product, prepared as a pseudoglobulin fraction from rabbit plasma, has been found moderately effective, particularly when applied fresh from powdered material.⁶² Other perhaps more potent preparations are now in process of manufacture from both human and bovine sources. For internal bleeding in hemophilia, for bleeding in joints and for severe local and external bleeding, *fresh* whole blood, citrated or unmodified, is quickly effective. Bank blood must not be used. Dry plasma prepared from fresh liquid plasma is apparently just as effective as fresh blood⁶³; however, this type of dried plasma is not commercially available.

The value of oxalic acid and of injections of shepherd's purse is still highly questionable. Shepherd's purse is a common weed that according to Copley and Lalich⁶⁴ was used centuries ago as a hemostatic agent locally and internally. They state that this plant or its extracts when taken orally may exert a hemostatic effect.

Emergency and even elective surgery may be done in hemophilia if the patient is properly prepared by transfusions given prior to, during and after operation. In a recent case at the Boston Floating Hospital, a hemophilic child aged three required a mid-

thigh amputation because of gangrene of the foot resulting originally from a fall, with bleeding into the leg. The amputation was successfully carried out by dint of numerous transfusions, given both before and after operation. Baird and Fox⁶⁵ report a case of severe paratracheal hemorrhage in a hemophilic child, with recovery following tracheotomy, in which the bleeding was controlled by the use of large quantities of blood. Although the patient was only four and a half years old, the initial quantity of blood given was 950 cc., and this was followed by the daily administration of 500 cc. of blood for three days.

Hypoprothrombinemia. Two types of hypoprothrombinemia must now be discriminated: a clinical type that is the result of various etiologic factors and an artificial type that can be conveniently produced by the administration of dicoumarin. The development of knowledge regarding prothrombin deficiency and its relation to vitamin K represents a fascinating chapter in modern medicine. Hypoprothrombinemia is now known to occur as the result of severe dietary deficiency, in conditions of intestinal disease and malabsorption, in the newborn infant because of the lack of a beneficial intestinal bacterial flora, in severe hepatic disease and in obstructive jaundice.⁶¹ There has furthermore been described a condition of idiopathic hypoprothrombinemia in which the presence of a hemorrhagic disorder is associated with a greatly increased prothrombin time, although none of the above etiologic factors are present.⁶⁶ The treatment of hypoprothrombinemia has been fairly well standardized. Except in severe hepatic disease and perhaps in the idiopathic type, vitamin K is equally effective whether given orally, intramuscularly or intravenously. The routine use of the vitamin just before delivery has been widely recommended as of value in reducing the prothrombin time of the fetus. This method has much to recommend it because even though the mother is normal, the newborn infant may show a delayed prothrombin time. The presence of even incipient hemorrhagic disease may well contribute to cerebral hemorrhage, particularly if the delivery is a difficult one. On the other hand, Parks and Sweet⁶⁷ found no greater incidence of hemorrhagic disease in infants born of mothers who received no vitamin K antenatally than in those born of mothers who had received 5 mg. of the vitamin orally on admission to the hospital. Despite this report, it is probably best to give the mother 5 to 10 mg. of vitamin K intramuscularly just prior to delivery, thus ensuring an adequate prothrombin concentration in the fetus during its more or less arduous journey through the birth canal.

The prothrombin time is usually performed by the method of Quick, using rabbit brain as a source of thromboplastin. Fullerton,⁶⁸ and later Page and his collaborators,^{69, 70} have introduced the use of solutions of Russell viper venom (Stypven — Burroughs

Wellcome and Company) as a substitute for rabbit-brain thromboplastin. Page and de Beer⁷⁰ state, "The commercially available venom is convenient, quite uniform within and between batches, and, as originally packaged, stable for at least five years." The solutions retained their thromboplastin-like activity unimpaired for months at icebox temperature but suffered decomposition after about two months' exposure to the air at room temperature. Lyophilized rabbit brain as a source of thromboplastin is extremely potent and is now commercially available. Fractions sealed in vacuo and kept in the dark at 3°C. have, according to Hoffman and Custer,⁷¹ kept their potency for at least seventeen months. The latter authors describe a micromethod for the estimation of prothrombin in fresh capillary blood; although the test appears to be very accurate, it requires much special apparatus including a special pipette, a specially constructed heating unit and slide holder and a platinum rake.

The use of dicumarol to prolong the prothrombin time and total coagulation time was introduced by Bingham, Meyer and Pohle⁷² in the prevention of thromboses and as a substitute for heparin in other conditions. Bingham, Meyer and Howard⁷³ report that the drug should be used with caution and is contraindicated in patients with hemorrhagic tendencies or gross hepatic disease. The usual dosage was an initial administration of 5 mg. per kilogram of body weight, followed by a daily dose of 1.5 mg. per kilogram. On certain days no dose was given if the prothrombin time or coagulation time was too prolonged. Since there is a latent period in the development of delayed prothrombin and total coagulation times, heparin has been advantageously used for its immediate effect. To employ these measures with safety to the patient, the daily determination of prothrombin and coagulation times is imperative; the prothrombin concentration should be no lower than 25 per cent of normal, and the coagulation time should be no greater than fifteen to twenty minutes. Davidson and MacDonald⁷⁴ caution against the indiscriminate use of dicumarol. They found vitamin K of no effect as an antidote, and whole-blood transfusions had either no or only a transitory effect on the abnormal clotting mechanism in patients receiving the drug. Large-scale clinical studies have been made by Allen, Barker and Waugh⁷⁵ at the Mayo Clinic. Of 374 patients who were given the drug postoperatively to prevent thrombosis, only 3 developed thrombophlebitic lesions. The dicoumarin was administered orally, single doses of 200 to 300 mg. being given on the first day and 200 mg. on the second day. Subsequent daily dosage is based on the prothrombin time of the blood drawn that day, keeping the latter between thirty-five and sixty seconds. Wright and Prandoni⁷⁶ conclude that the therapeutic value of dicoumarin has as yet not been clearly established.⁷⁷

HEMOLYTIC SYNDROMES

As noted in the 1942 review, the hemolytic syndromes may be classified as acquired and hereditary, with a special grouping for hemoglobinurias. Familial spherocytosis (congenital or familial hemolytic anemia) is by no means the only type of hereditary hemolytic disease, since two other well-defined syndromes are present: a Mediterranean target-oval cell condition and sickle-cell anemia. The hemoglobinurias have been well described, and are of the following varieties: paroxysmal cold, paroxysmal nocturnal and march; in addition, hemoglobinuria regularly occurs in the presence of sudden intravascular hemolysis when the threshold value for hemoglobin in the plasma is exceeded.

Mechanisms

The mechanisms that initiate and carry through normal red-cell destruction are quite obscure, although one may speak of possible swelling and fragmentation of the red cell and of its total destruction in the reticuloendothelial system, more particularly in the spleen. In the acquired hemolytic types, it becomes more and more apparent that attempts to implicate some one mechanism such as agglutination, erythrosthesis or the activity of hemolysins stretch the point, since diverse mechanisms can all bring about the dissolution of the red cell.

Dameshek and Miller⁷⁸ studied the effects on red cells of simple lysins, complex hemolysins and agglutinins. Simple lysins act directly on the red cells, producing either complete hemolysis or spherocytosis. Complex hemolysins, such as immune hemolysins, first produce sensitization — that is, agglutination — by means of amboceptor and then hemolysis by means of complement. Agglutinins produce agglutination that results in hemolysis, probably because of several factors, important among which is that of mechanical trauma within the circulation. Both hemolysins and agglutinins act by injuring the red cells actively — the final stage of hemolysis taking place by different mechanisms. Other factors that are undoubtedly of importance are such physical ones as temperature and hydrogen-ion concentration.

In this paper, Dameshek and Miller contrast their "active" concept of hemolysis with the more "passive" one of erythrosthesis of Ham and Castle.⁷⁹ The latter investigators have stated that the hemolytic anemias are due to agglutination of red cells with subsequent stasis, to increased viscosity with stasis or to increased rouleaux formation with stasis. In other words, the feature most stressed is that of stasis. Yet in multiple myeloma, in which rouleaux formation is often extreme, and in polycythemia, in which stasis and viscosity are both very marked, hemolytic anemia rarely if ever occurs. Furthermore, such explanations are of no value in cases with a circulating autohemolysin, in paroxysmal cold hemoglobinuria, in paroxysmal nocturnal hemo-

globinuria and so forth. What is more, Shen, Han and Fleming⁸⁰ have recently demonstrated that the heating (and possibly searing) of red cells under conditions of severe burns is followed by spherocytosis and hemolysis. This is in line with Dameshek and Miller's previous investigations, which demonstrated that spherocytosis — the forerunner of hemolysis — can be experimentally produced by a variety of chemical, immune-body and physical agents. Napier and Sen Gupta,⁸¹ working in India have recently confirmed in monkeys this experimental work on hemolysins and hemolytic anemia in guinea pigs. The development of spherocytosis and of double-peaked Price-Jones curves is also described, together with careful statistical analysis of the data. Napier and Sen Gupta make the observation that although the life of the spherocyte may possibly be shorter than that of a normal cell, it cannot be considered as an immediate precursor of hemolysis. For this, other mechanisms (possibly the spleen) may be necessary. Spherocytosis is by no means pathognomonic of familial hemolytic anemia but occurs in many conditions, familial and acquired, in which active hemolysis is present. Thus, it is characteristically seen in the acute hemolytic anemia of sulfonamide administration.

The occurrence of hemolytic anemia in association with a circulating cold hemagglutinin has occasioned much recent interest. In 3 cases that I¹⁶ reported, sulfonamides had been given and it was difficult to state whether the sulfonamide had directly produced the hemolytic anemia, whether it had not been concerned at all or whether the combination of sulfonamide and agglutinin was responsible for the anemia. Some cases of acute hemolytic anemia have apparently arisen in primary atypical pneumonia simply in association with a high titer of cold hemagglutinin.¹³ We have recently been studying a patient who has a chronic hemolytic process in association with a very high concentration of cold hemagglutinin. Stats and Wasserman¹² in their recent exhaustive review of cold hemagglutination discuss the possibility that hemolysis occurs in such cases through the medium of mechanical trauma of agglutinated red cells.

Tompkins⁸² discusses the effects of repeated intravenous injection of lecithin in rabbits and their relations to lipid-storage diseases and to hemolytic anemias. The lecithin not only accumulates in the reticuloendothelial system, more particularly in the spleen, but results in a slowly progressive hemolytic anemia associated with a slight increase in hypotonic fragility and an increased malleability of the cells, with a tendency to the formation of oval and even sicklelike forms. This effect may have some relation to normal hemolytic mechanisms because of the possibility that phospholipids in the circulation are adsorbed on erythrocytes and because lecithin is a well-known hemolysin. It is also in line with the

work of Freeman and Johnson,⁸³ who believe that lipid materials by entering the thoracic duct go indirectly into the circulation and affect the red cells by gradual swelling and finally hemolysis.

Also related to this general concept is the work of Collier, Allen and Swales.^{84, 85} In studying phenothiazone, which is used as an anthelmintic in horses, these investigators found that although it produced hemolytic anemia *in vivo*, it failed to do so *in vitro*. This chemical, however, had a strikingly accelerating effect on the lysis of red cells by saponin or lysolecithin, and the authors state that this property may be responsible for its *in vivo* effect in cases in which some lysolecithin is presumably present. Lee and Tsai⁸⁶ point out, however, that lecithin may be antihemolytic as well as hemolytic, this being dependent on such factors as concentration of cholesterol and temperature. Finally, Ponder⁸⁷ discusses the disk-sphere transformation produced by lecithin. It can easily be seen that much clarification is required for the mechanisms underlying hemolysis, even under normal conditions.

Clinical Syndromes

Hereditary types. Of the three hereditary forms of hemolytic anemia, *familial spherocytosis* is by far the best known; in fact, the term "congenital hemolytic anemia" is often applied to this well-defined condition, in which spherocytosis, increased hypotonic fragility and prompt cure by splenectomy are important features. The cause of the spherocytosis has not been established, although, since this abnormal red-cell feature can be so readily produced by the action of hemolysins, it seems logical to conclude that an abnormal hemolytic mechanism of some sort is present. Dacie and Mollison⁸⁸ showed that when normal red cells are introduced into the circulation of these patients, they have a normal survival time; conversely, spherocytes introduced into a normal person's circulation quickly disappear. Although these authors concluded that the basic abnormality is abnormal erythrocyte formation, the role of possible hemolytic mechanisms cannot be excluded, since it would naturally be expected that spherocytes, already being, so to speak, on the road to hemolysis, are more quickly destroyed in the intact spleen. In a further paper, in which curves of hypotonic fragility, the histology and physiology of the spleen and so forth are carefully analyzed, Dacie⁸⁹ showed that the spleen is unusually congested. Perfusion experiments with excised spleens did not demonstrate the cause of the congestion. Dacie concluded that the available evidence points to the presence of a hemolytic disorder based on abnormally hemolyzable red cells, and that the possibility of the presence of an abnormal hemolytic agent or metabolite cannot be ignored. This leaves the problem about where it was originally.

The presence in people of Mediterranean origin of anemia of varying degrees of severity, often show-

ing apparently different clinical syndromes — from the severe and fatal Cooley's anemia to a mild hypochromic anemia or hypochromic erythrocytosis — has been discussed in previous reviews, and is described under the designation, "familial Mediterranean target-oval-cell syndromes," in a recent article.⁹⁰ These conditions appear to have as one of their fundamental characteristics an inherited abnormality of hemoglobin formation, with the result that the red cells are unusually thin and have the appearance of targets or bull's eyes in the stained blood films. Oval and elliptical cells are also frequent. Because the red cells are unusually thin, they are, in contradistinction to the spherocytes, abnormally resistant to solutions of hypotonic sodium chloride. Despite the hypochromic character of the anemia in most cases, there is no response to iron — apparently because the nucleated red cell cannot make or deposit sufficient quantities of hemoglobin within its cytoplasm. More severe cases have a hemolytic component, with icterus, splenomegaly and increased urobilinogen output present. Bone changes are found only in the most severe forms. In this paper, and in an exhibit at the 1942 meeting of the American Medical Association,⁹¹ the numerous resemblances between the essentially Mediterranean target-oval-cell syndromes and the essentially African (Negro) target-sickle-cell syndromes were pointed out. In both these conditions, unusual thinness of the red cells (leptocytosis) is prominent, with complete refractoriness to iron therapy. In both, it appears that the mating of two persons each of whom has a mild condition or trait may result in the presence of a severe condition in one or more of the offspring.

Smith⁹² confirms most of these findings in a study of sixteen families, and points out that recognition of the mild type depends solely on a careful study of the blood. This author objects to the designation of "target-cell anemia" for these cases, since target cells are by no means constantly present and are non-specific. Since, however, increased hypotonic resistance was always present, it is certain that the red cells were unusually thin, which amounts to the same thing. Leptocytosis, which indicates the presence of thin as opposed to thick red cells (spherocytes), may be a better designation. Familial leptocytosis is by no means nonspecific, although it must be conceded that target cells *per se* may occur in a number of diverse conditions.

That target-cell anemia may not be completely limited to people of Italian, Greek, Syrian or Portuguese origin is brought out by Schieber,⁹³ who reports 2 cases in a family of Buchara Jews. The author states that the ancestors of these people have been known to live on the shores of the Caspian Sea for many centuries, although in the dim past they must have originally wandered up from the Levant.

More and more cases of *sickle-cell anemia* are being reported in the white race, more particularly

in those of Italian origin. Morrison, Samwick and Landsberg⁹⁴ point out the common difficulties encountered in making the diagnosis of sickle-cell anemia in white people. Search for the sickling phenomenon, they say, should be undertaken in all cases of obscure hemolytic disorders, even in white patients. They state that in the presence of splenomegaly, a splenic puncture may demonstrate a far more marked sickling phenomenon than does the peripheral blood. Greenwald, Spielholz and Litwins⁹⁵ make similar observations and point out the relatively frequent occurrence of sickle-cell anemia among people of southern Italian and Mediterranean descent. Ogden⁹⁶ reports 9 cases of the sickling trait — 2 of them active sickle-cell anemia — in two white families. On the assumption that sickle-cell anemia is a national public-health problem, the author comes to the radical, possibly biased, conclusion that "intermarriages between Negroes and Whites directly endanger the white race by transmission of the sickling trait. . . . Such intermarriages . . . should be prohibited by federal law."

Acquired hemolytic disease. It becomes increasingly clear that most of the cases of hemolytic disease are not hereditary, but are due to a variety of etiologic factors, including hemolysins of immune body type, agglutinins, chemicals, bacteria and other organisms such as the malarial parasite. Some of the cases occur in association with a more fundamental disease (Hodgkin's disease, lymphoma and so forth). Singer and Dameshek⁹⁷ have termed these "symptomatic." Hemolytic disease of whatever cause is due to the breakdown of red cells, with the rapid liberation of hemoglobin (hemoglobinemia and hemoglobinuria) or its slow conversion into bilirubin. As direct evidences of increased hemolysis, Dameshek and his co-workers⁹¹ list the following: anemia, indirect bilirubinemia, hemoglobinuria, increased red-cell thickness, — that is, spherocytosis, — increased hypotonic fragility of the red cells and increased output of urinary and fecal urobilinogen. Of these features, the fecal urobilinogen output is by far the most important and most direct evidence of increased hemolysis; all the other features may be present in the absence of increased blood breakdown.⁹⁸ Indirect evidences of increased hemolysis are shown by increased bone-marrow activity, particularly by reticulocytosis and polychromatophilia, leukocytosis, polymorphonuclear and platelet increase and splenomegaly. Clinically, the combination of pallor and icterus should always make one suspect a hemolytic process, particularly if splenomegaly is present. Careful examination of the stained blood smear often shows the combination of small, thick, dense-appearing red cells and of large red cells that are bluish gray (polychromatophilic). The spherocytes indicate hemolysis; the large polychromatophilic cells (reticulocytes) indicate active regeneration on the part of the marrow.

Wilson and Mangun⁹⁹ report 3 interesting cases of acute hemolytic anemia with hemoglobinuria in fertilizer workers who were exposed to fumes decaying fish and impure sulfuric acid. In the hold of the ill-ventilated boats into which these men were sent, it is probable that arsine gas was generated. Arsine has long been known as a strong hemolytic agent. Wilson and Mangun demonstrated an active hemolysin in the globulin fraction of the serum; since complement was not necessary, this was not of the immune-body type. They postulated that the arsine gas, entering the lungs, entered into a loose combination with blood protein, so altering it as to give it an active hemolytic property, independent of the presence of arsenic itself. An important clinical fact brought out in these cases is the necessity for maintaining an alkaline urine in cases with hemoglobinuria to minimize precipitation of hemoglobin products in the renal tubules.

Acute hemolytic anemia of the newborn — erythroblastosis fetalis — is apparently due to an agglutinative-hemolytic reaction between the anti-Rh agglutinin of the mother's serum and the newborn infant's Rh+ red cells. Dameshek, Greenwald and Tat¹⁰⁰ found that the output of fecal bilirubin and urobilinogen was distinctly increased in these cases; all the other indications of an acute hemolytic process were also present, including biphasic Price-Jones curve of red-cell diameter, marked regenerative activity on the part of the bone marrow and so forth. Reisner,¹⁰¹ who studied the red-cell diameters of 12 cases of fetal hydrops and of icterus gravis, found in all but 1 characteristic biphasic curves resembling those observed in experimental hemolytic anemias due to antigen-antibody reactions; it is probable, as stated above, that similar mechanisms are operative in the human cases. Transfusions with Rh- blood are often quickly effective in controlling the anemia and resulting in a favorable therapeutic result. If the mother is known to be Rh-, it is certainly wise to have Rh- donors on hand for possible immediate use in the newborn infant.

I¹⁰² have recently stated my views on the management of acute hemolytic anemia and the hemolytic crisis as based on the study of 25 cases. Such cases are serious therapeutic problems demanding careful and sustained attention. Unusual heed must be paid to blood-grouping technics, and search must be made for atypical hemolysins and agglutinins. Because of the possibility of reactions to as few transfusions as possible should be given. Immediate consideration of splenectomy should be taken up, since continued procrastination in the hope that something will turn up may result in a blind alley from which there may be no escape but splenectomy done as a desperate measure of last resort. The familial cases in crisis uniformly do well with splenectomy, but in the acquired cases prediction as to ultimate recovery is difficult. In 1

quired cases, 10 patients made a full recovery after operation and 8 died — 4 of them from continued emolysis. Some of the deaths may well have been preventable, perhaps by earlier operation. This rather high mortality rate with splenectomy must be weighed against the almost 100 per cent mortality of expectant treatment.

Hemoglobinurias. The hemolytic diseases characterized by outspoken hemoglobinuria are perhaps best considered separately. They usually indicate a different type of hemolysis from the acute, subacute and chronic hemolytic anemias, in which hemoglobin is converted to bilirubin in the cells of the reticuloendothelial system. The rapid intravascular destruction of hemoglobin leads to hemoglobinemia, which if it exceeds the renal threshold of hemoglobin (approximately 150 mg. per 100 cc of blood) results in hemoglobinuria. Cold hemoglobinuria is usually associated with tertiary syphilis and the presence in the blood of an autohemolysin may, however, be due to a high concentration of cold hemagglutinin, as recently observed in one of my cases. In paroxysmal nocturnal hemoglobinuria, the red cells are unusually sensitive to dilute acids, perhaps because of the activity of a peculiar hemolysin. In march hemoglobinuria, appreciable quantities of blood are broken down (possibly in the kidneys) by long walks or runs. Much more frequent than these conditions, however, are the hemoglobinurias of transfusion reactions and the blackwater fever of malaria. Hoffman and Kracke¹⁰³ review the hemoglobinurias and discuss their diagnosis and differentiation.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30181

PRESENTATION OF CASE

First admission. A twenty-six-year-old housewife was admitted to the hospital because of abdominal pain.

The patient had been in good health until about twenty-one months before entry, when, following a two-day history of epigastric pain gradually localizing in both lower quadrants and associated with severe cramps on urination and one episode of vomiting, she was admitted to a community hospital. A pelvic abscess was drained through the vagina, and vaginal smears were said to have shown many gram-negative diplococci. About a month later a right subphrenic abscess was incised in the same hospital, and she was finally discharged after two months. She was then fairly well until seven months before admission, when she underwent an appendectomy in the same hospital. She remained in moderately good health until two months prior to entry, when she developed a dull grinding ache in the lower abdomen. Abdominal exploration at that time showed an absolutely "frozen" pelvis and many adhesions between the intestines. While the adhesions were being separated a small opening was made in a loop of small intestine. This was closed. She recovered from the operation and was discharged home. Two weeks before admission to this hospital she developed severe, crampy, low abdominal pain, which was associated with nausea but no vomiting or changes in the bowel habits. There was considerable pain in the back, urinary frequency and leukorrhea.

Physical examination showed a well-developed, fairly well-nourished woman. The heart and lungs were normal. There was a firm, tender, suprapubic mass, which extended higher on the left than on the

right. Pelvic examination showed a small cervix. The uterus was forward, freely movable and not attached to the mass. The mass was tender, "in and out of the pelvis" and probably cystic.

The blood pressure was 112 systolic, 75 diastolic. The temperature was 99.6°F., the pulse 70, and the respirations 20.

Examination of the blood showed a red-cell count of 3,600,000, with 10 gm. of hemoglobin. The white-cell count was 21,400, with 70 per cent neutrophils. An intravenous pyelogram was negative. Above the bladder there was an enlarged shadow having the appearance of an enlarged uterus. In connection with this there was an ill-defined, soft-tissue shadow extending out of the pelvis, especially to the left. A barium enema showed the same mass displacing the sigmoid to the left. A tuberculin test in dilution of 1:100,000 was negative.

The patient continued to have abdominal pain. A Miller-Abbott tube was passed, with considerable relief. She was given several transfusions and 12.5 gm. of sulfasuccidine daily, and on the eighth hospital day a laparotomy was performed. The small intestine was matted down in the midabdomen by many adhesions. The uterus, both tubes and ovaries appeared normal. The left ovary was slightly enlarged. It was impossible to mobilize the sigmoid. Both the sigmoid and bladder were accidentally opened and sutured, and the abdomen was closed. Peritoneal culture was negative. She had a slightly stormy postoperative course and was given several transfusions and 4 gm. of sulfadiazine daily. She was discharged on the fifteenth postoperative day.

Second admission (three months later). Following discharge the patient continued to have bouts of sharp, steady, low abdominal pain, pain in the bladder on urination and occasional bouts of fever (102°F.) with chills. The vaginal discharge continued.

Physical examination showed marked tenderness in both lower quadrants, more on the right than on the left, without much spasm. A poorly defined moderately tender mass was present in the left lower quadrant. Pelvic examination revealed pain and tenderness on motion of the cervix. In the left vault was a tender soft mass that seemed to rise out of the pelvis to the umbilicus. The right vault was clear but tender.

The blood pressure was 116 systolic, 72 diastolic. The temperature was 100°F., the pulse 70, and the respirations 20.

*On leave of absence.

Examination of the blood showed a red-cell count 3,720,000, with 65 per cent hemoglobin. The white-cell count was 14,150. The urine was normal, as a roentgenogram of the chest. A tuberculin test in dilution of 1:1000 was negative.

The patient was given several transfusions, placed on a high-calorie, high-vitamin diet and discharged to a nursing home.

Final admission (five months later). Following discharge she continued to have episodes of low abdominal pain. She lost about 15 pounds of weight and was bedridden most of the time. She drained considerable purulent material from the vagina, requiring five pads daily. Two or three days before surgery she began to have increasingly severe, constant, right lower abdominal pain. There were no anorexia and some nausea, but no vomiting.

Physical examination showed a pale, thin woman who looked chronically ill. Exquisite tenderness and spasms were present over the right lower quadrant, where a round mass about the size of a grapefruit was palpable. Pelvic examination showed a profuse purulent discharge, a large tender fluctuant mass on the right and a firm, apple-sized, tender mass on the left.

The blood pressure was 94 systolic, 54 diastolic. The temperature was 102°F., the pulse 110, and the respirations 24.

Examination of the blood showed a red-cell count of 3,250,000. The white-cell count was 23,800. The urine gave a + test for albumin, and the sediment contained 30 to 40 white cells per high-power field.

The patient was given a transfusion of 500 cc. of whole blood. Incision and drainage of a pelvic abscess was done vaginally, yielding 200 cc. of foul thick pus on the left and a small amount of clear straw-colored fluid on the right. On the fourth hospital day incision and drainage of the abscess in the right lower quadrant was done, yielding a moderate amount of thin, clear, yellow-red fluid. Both cultures showed a few colonies of *Staphylococcus albus* and of nonhemolytic streptococci. Drainage through the vagina was profuse. The patient continued to have a fever of 101 to 102°F. She was treated with an abdominal heat cradle, repeated transfusions and sulfadiazine.

On the thirty-first hospital day an exploratory laparotomy was performed.

DIFFERENTIAL DIAGNOSIS

DR. WALTER E. GARREY: The first laparotomy on her is helpful, because they apparently did get through the dense adhesions that had been found previously in the community hospital only to find that the uterus, tubes and ovaries were normal.

May we see the x-ray films?

DR. MILFORD SCHULZ: This is one of the films of a roentgenogram and shows an essentially normal upper urinary tract; there does seem to be a soft-tissue

mass arising in the left side of the pelvis. Here is another film with a curious metallic foreign body with an accretion about it lying in the pelvis, not in the bladder or in the uterus. It is present in all the films.

The film of the chest is merely confirmatory of negative findings.

DR. GARREY: I believe the best way to handle this case is to jump in feet first and try to account for the disease of the peritoneum that caused dense adhesions, a friable bowel, because of which several operators entered the small bowel, large bowel and bladder in their efforts to separate the adhesions, and loculated collections of fluid, which seem to have varied in their character and in their location from time to time.

Before I saw the x-ray films I thought this woman had tuberculosis of the peritoneum, although I should have to account for the negative tuberculin test. I still think so, but I had not heard about this metallic foreign body. In seeking for the cause of a foul purulent discharge and recurring foul abscesses low in the pelvis, foreign body is one of the first things that come to mind. It is possible that some part of a drain or other material had been introduced during one of the earlier operations and had persisted in the cul-de-sac as a foreign body. If that were the case, I believe we should have to make a double diagnosis, tuberculosis and foreign body. So much for what seems the most likely possibility.

The pelvic causes are reasonably well ruled out by the operator who saw the pelvis when the patient was operated on in this hospital. It is inconceivable that she had a gonococcal pelvic peritonitis and salpingitis at the time of the first operation, a little over a year and a half before she came in. Could she have had such an infection and not have had visible damage in the tubes and perioophoritis? I doubt it. I also think it unlikely that the gonococcus could have caused subphrenic abscess, although it may even cause perihepatitis. Perhaps the gram-negative organisms that were allegedly found at the other hospital were due to gonococcal infection of the lower genital tract. Perhaps they were not truly gram-negative diplococci of the gonococcal variety. I think, but this is only a guess, that the appendix was probably the cause of all this trouble and that they later took it out, as one does for a perforated appendix in which the abscesses have been previously drained.

Of course endometriosis is a cause for dense adhesions and persistent trouble in the lower abdomen, but such a diagnosis is ruled out by the examiner who found normal adnexa at operation.

An infected dermoid cyst came to my mind as a cause for persistent pus. Perhaps such a cyst ruptured and spilled out its contents; but that is most unlikely. If she had had hydatid disease scattered through the abdomen, we should have heard some

mention of a well-encapsulated cyst rather than the story of dense and matted adhesions. I do not believe that the persistent fluid collections in the lower abdomen were caused by an intrinsic lesion of the gastrointestinal tract. The patient was not of the age group in which diverticulitis is commonly found, and nothing of this nature was noted on barium enema at the first entry.

Regarding neoplasm, one can remotely conceive that she had a mucous cyst of the appendix that had ruptured at the early operation and that pseudomyxoma spread through the abdomen, but I believe that they would have found some of the myxomatous material at operation here and that we should have heard of it in the findings that are given us.

If she had a tuberculous peritonitis, would it be possible for her to have had a negative tuberculin test, once in a high dilution and once in a fairly concentrated dilution? I think that it would be if she had a persistent focus of infection and had thus been able to desensitize herself. I have been told that terminal and fairly massive cases of tuberculosis often give a negative tuberculin test. Is that correct, Dr. Means?

DR. J. H. MEANS: I think so.

DR. GARREY: So I think that the patient did have a tuberculous peritonitis to account for the abdominal masses, the clear, free fluid and, later, the draining free fluid, the dense adhesions and the friable bowel. Perhaps she had a fistula in the sigmoid that communicated with a caseous mass. It also looks as if there was a foreign body, which may have been at the bottom of the last episodes, particularly the pelvic abscesses.

My diagnosis is tuberculosis of the peritoneum and probably a foreign body in the lower abdomen.

DR. MEANS: Is there any possibility of actinomycosis rather than tuberculosis? There was a lot of pus.

DR. GARREY: I thought of that and should have mentioned it. If she had had actinomycosis of this long duration there should have been extensive tissue destruction, and an actual fistula to the outside should have developed as a result of the destructiveness of that process.

CLINICAL DIAGNOSIS

Chronic pelvic inflammatory disease.

DR. GARREY'S DIAGNOSES

Tuberculosis of peritoneum.

Foreign body in pelvis?

ANATOMICAL DIAGNOSIS

Actinomycosis of fallopian tubes and ovaries.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: At operation the uterus and both tubes and ovaries were removed.

The tubes were thick and dilated and covered by firm fibrous adhesions, the right one more so than the left. The right ovary was intimately adherent to the tube and was enlarged. When this was cut into a fair amount of dirty gray, somewhat purulent material exuded; similar material was also found on the tube. Microscopic examination showed the lumen of the tube to be full of pus and scattered colonies of actinomycetes. The latter were also found in the ovary.

DR. LELAND S. MCKITTRICK: The medical department is doing well.

DR. CASTLEMAN: I believe that at the time of first admission here Dr. Arthur W. Allen suggested actinomycosis; the organisms were hunted for but not found.

DR. GARREY: How long do you think she had actinomycosis?

DR. CASTLEMAN: I do not know. It is a bit surprising that there were not more lesions in the pelvis at the time of the first operation here, but there were so many adhesions that apparently they were unable to explore the pelvis thoroughly.

What do you think about the origin, Dr. McKittrick?

DR. MCKITTRICK: I was wondering where it came from. There is the first episode to explain. She might have had a perforated appendicitis at that time and that might have been the origin of actinomycosis. Is that possible?

DR. CASTLEMAN: That is my feeling.

DR. MCKITTRICK: The whole story is a more or less confusing affair, but that is a possible explanation. Actinomycosis certainly follows, at least infrequently, work on the bowel, particularly operation for perforation of the appendix.

DR. CASTLEMAN: It is interesting that during the last two months we have had three cases of actinomycosis.

CASE 30182

PRESENTATION OF CASE

A fifty-nine-year-old business executive was sent to the hospital by his physician because of acute difficulty in breathing.

The patient had been in excellent health and a very hard worker until six years before the present episode when he developed "leg ache," insomnia and tiredness. He was seen by his physician who found a slightly enlarged heart. There was bigeminy and a rough apical systolic murmur. The blood pressure was 150 systolic, 70 diastolic. The white cell count was 7900, with 64 per cent neutrophils. The red-cell count was 4,810,000, with 80 per cent hemoglobin. The nonprotein nitrogen was 33 mg. per 100 cc. The urine was normal. A blood Hinton test was negative. An electrocardiogram showed a normal rhythm, with a rate of 68. The PR interval

as 0.16, and the QRS interval 0.07 second; T_1 and T_2 were upright, T_3 diphasic and T_4 inverted. There were slight left-axis deviation and ventricular extrasystoles. The T waves in Lead 2 were somewhat abnormal (there was a possibility that the lead wires in Lead 1 were crossed).

The pain in the legs continued; he was seen by various specialists during the following two years and obtained slight improvement by a leg bandage. Four years before the present episode he developed pain in the low back, and finally had an operation on a ruptured intervertebral disk, with apparent improvement in the back pain. The pain in the calves persisted, however, even with high-calcium therapy. An electrocardiogram one year before the present attack showed the same recording as before. There were frequent ventricular premature beats. The T waves were upright. Some slurring and prolongation of the QRS complex was seen. A chest roentgenogram six months before the present illness showed slight cardiac enlargement. The heart was a little wide across the auricles.

The patient remained in an essentially unchanged condition until five days before the present episode, when, after running for a train, he became breathless. In the next few days he had several attacks of mild dyspnea. One morning after severe dyspnea of four hours' duration, which had awakened him from sleep, he called his family physician.

Physical examination showed a well-developed, well-nourished, moderately dyspneic man. The cervical veins were slightly prominent. The left border of cardiac dullness was 9 cm. to the left of the midsternal line in the fifth space. The rate was irregular, with frequent extrasystoles. The pulmonic second sound was greater than the aortic. A loud (Grade IV) harsh, apical, systolic murmur was transmitted posteriorly. There was a slight thrill at the apex, but no gallop rhythm. The pulse was full. Examination was otherwise negative. The blood pressure was 130 to 160 systolic, 70 diastolic. The apical pulse was 84, the radial pulse 72. The temperature was normal.

Examination of the blood showed a hemoglobin of 90 per cent. The white-cell count was 7400, with 54 per cent neutrophils.

He was given 0.1 gm. of morphine hydrochloride, with instantaneous relief. He had a second, but much milder, attack of breathlessness at 5:00 o'clock the next morning, and three mild attacks the following day. He was then placed on $1\frac{1}{2}$ gr. of digitalis three times daily and on 3 gr. of quinidine three times a day for the irregularity. His condition improved definitely until the eighth day of his illness, when he had considerable air hunger associated with pounding and irregularity of the heart beat. Examination showed definite bigeminy, with the alternate beats not coming through. The rate at the wrist was 45. It was found that air hunger, irregularity of the rhythm and pounding appeared

when he lay down, but that these disappeared and bigeminy was resumed when he sat up. The digitalis was stopped because he had received a total of 18 gr. He developed pain in the legs, but no evidence of phlebitis could be found. In the next four days he had periods of quadrigeminal rhythm, — that is, three normal beats and then an extrasystole that did not get through to the wrist, — alternating with bigeminy and periods of air hunger and pounding when he slumped down. On the fourteenth day of his illness he was quite weak and complained of sleeplessness; he was given 50 mg. of Demerol. On the evening of the fifteenth day, while being read to by his wife, he complained of not being able to get his breath, took four or five gasps and died within a few seconds. When seen by his family physician a few minutes after that, no dilated neck veins were found.

DIFFERENTIAL DIAGNOSIS

DR. CONGER WILLIAMS: We are not told whether the leg ache resulted from exercise, when it occurred and so on. Such pain in the leg might mean the onset of intermittent claudication due to arteriosclerosis in the extremities, or it might mean thrombophlebitis. But I judge from the long duration and the absence of mention of swelling that the ache did not mean thrombophlebitis.

It is possible that the back pain was the result of a ruptured intervertebral disk, whereas the leg pain was due to peripheral arteriolar disease or thrombophlebitis.

Have we the x-ray films here?

DR. BENJAMIN CASTLEMAN: No; they were taken outside.

DR. WILLIAM B. BREED: Dr. Holmes interpreted the x-ray findings.

DR. WILLIAMS: "The patient remained in an essentially unchanged condition until five days before the present episode, when, after running for a train, he became breathless." This is the first sign of anything suggesting changes in the cardiac status. We have the statement that six years previously a loud, rough, apical systolic murmur was heard, which was still present at the time of this examination. The onset of dyspnea with exercise suggests cardiac failure. The subsequent attacks were not necessarily related to exercise.

We are told that the systolic murmur was transmitted posteriorly. I wondered about that statement. Does it mean transmission to the axilla or all the way around to the lung bases and back? That distinction is of some importance in making a differential diagnosis.

DR. PAUL D. WHITE: All the way around to the lung bases.

DR. WILLIAMS: The relation of bigeminal rhythm to posture is interesting. Change in position with assumption of the horizontal would make the more breathless, and might speed up the

pulse rate. With a faster pulse and shorter diastole, premature beats are less likely to occur. We know that he had previously had an irritable ventricle and was subject to attacks of ventricular premature beats. It might be that posture, either through its effect on congestive failure or possibly from reflex effect, modified in some way the formation of premature beats. It is well known that certain cases with tachycardia are affected by posture. I have seen the frequency of formation of ventricular premature beats altered by a change in position.

In considering the differential diagnosis I think that we have rather good evidence for the existence of heart disease. Can the whole picture be explained by assuming that he had heart disease alone, or must we assume that he had other complications in addition to heart disease? Certainly the presence of a loud apical systolic murmur over a period of six years is good evidence for heart disease, and in a man of this age the presence of such a murmur, even though it is not heard in the aortic area, always makes one suspicious of aortic stenosis. This is particularly true in the presence of emphysema, when the base of the heart may be some distance from the sternum, interfering with the transmission of the murmurs to the aortic area. It does not happen so often in thin patients. Another thing that inclines me to a diagnosis of aortic stenosis is the clinical course. In the first place he had only slight, apparent enlargement by x-ray examination six months before the final episode began. In aortic stenosis one may get considerable hypertrophy of the ventricular wall before any enlargement becomes evident by x-ray. The fact that he had few symptoms until the time of the final episode is consistent with aortic stenosis. The blood pressure in this case was not the typical blood pressure of advanced stenosis of the aortic valve, but that again does not rule out the diagnosis because it may occur in association with hypertension. Another thing in favor is the rather indefinite character of the electrocardiogram. It certainly did not give any specific diagnostic lead, most of the abnormality occurring in Lead 2 or 3. Aortic stenosis may give a variable electrocardiographic picture. It often is not of much help in making a diagnosis, and may not show evidence of left ventricular strain. Certainly this electrocardiogram did not show left-axis deviation, and did not have the characteristics of left ventricular strain. Another thing in keeping with the diagnosis is sudden death, patients with high-grade aortic stenosis often dying suddenly. Of course some are prone to fainting attacks, but it is not necessary in patients who die suddenly from this disease to have had previous fainting attacks.

The fact that the murmur was heard in the back is against the diagnosis of aortic stenosis. Well-transmitted aortic systolic murmurs are heard in the axilla but not in the back. Also against the

diagnosis is the fact that the aortic second sound was heard. That does not rule it out, however.

If the patient did not have aortic stenosis, what caused the apical systolic murmur? I am not able to say. I believe that he almost certainly did not have mitral regurgitation on the basis of old rheumatic infection. My main argument against that is the fact that at no time did he show evidence of marked left ventricular enlargement. Had such a lesion been present for several years, particularly a lesion of sufficient degree to produce a murmur this loud, one would expect to see considerable enlargement, both of the left auricle and ventricle. The x-ray report states, "The heart was a little wide across the auricles." I assume that this was in the posteroanterior view. The auricles are not mentioned specifically, which is not particularly helpful.

One must consider the possibility of cardiac dilatation to explain the murmur, but there are several things against that. One is the duration. We know that the murmur had been present for six years, and yet the degree of cardiac enlargement was never very great. So I think we must assume that in all probability he had a valve deformity to account for this murmur. I find it hard to account for the murmur on the basis of any disease in the mitral valve, and I certainly can think of no congenital lesion that would fit in with this murmur and also with the findings in the electrocardiogram. I did consider the possibility of coarctation of the aorta, but certainly there is nothing to support that diagnosis. I also considered the possibility of whether this man had, in addition to a valvular lesion, coronary heart disease. It is quite likely that he did, although we have no objective evidence for it. One cannot, however, explain the cardiac enlargement and subsequent events on the basis of coronary heart disease alone. Ordinarily when one sees a significant enlargement of the heart in the course of coronary heart disease, there has been at least one myocardial infarction at some time in the past. We have neither electrocardiographic nor clinical evidence to support that diagnosis.

Then of course there is one condition outside of the heart which we must consider in any acute cardiac diagnosis — namely, pulmonary embolism. There are a number of things in this man's story and findings that suggest pulmonary embolism. In the first place we have a rather vague story of pain in the leg, which might have meant thrombophlebitis, although at no time was there objective evidence of such. It is possible to have large pulmonary emboli without any sign of thrombophlebitis in the leg; in fact it is a fairly common occurrence. That might explain the findings of distended neck veins, the loud pulmonic second sound and finally the sudden death, assuming that he had one embolus or more at the beginning of the final episode and another at the end. But I was not so satisfied with that diag-

is as I was with the diagnosis of heart disease to lay the whole thing. I still cannot think of anything that fits the findings quite so well as aortic regurgitation, in spite of the fact that the murmur was heard in the aortic area.

DR. BREED: When I first saw this patient a number of years ago I considered the distinct possibility of some congenital lesion. He was not really a cardiac patient until a short time before his death. I considered thrombophlebitis seriously, and I might think that this question of the pain he had in his legs could be corrected. It was not pain. It was a feeling of discomfort and tension in his calves, which kept him from sleeping. It should not be dignified with the name of pain.

There is another point that I think is important coming out: this murmur was sharply localized at the apex and was associated with a systolic thrill in the same area; the base of the heart was practically free from murmur and absolutely free from it. The murmur was transmitted directly up to the base of the left lung.

DR. WHITE: I wish Dr. Williams had been there with his stethoscope. It is sometimes impossible to hear murmurs adequately. You have to hear it. This murmur was practically entirely at the apex, and it was loud. I felt a slight thrill at the apex. The murmur was not heard along the upper back over the spine, but was well heard at the bases. I thought that that distinction was important enough to allow us to decide that the valvular defect was mitral regurgitation rather than aortic stenosis. Had Dr. Williams been there he would, I think, have voted for mitral rather than aortic origin of the murmur. In middle-aged and older men, however, aortic stenosis, rather than mitral regurgitation, is usually responsible for loud murmurs that have been present for years.

His patient had had no rheumatic history. He had his tonsils taken out as recently as 1937 and had had a life-insurance examination ten or fifteen years previously; but the murmur had been present for years before the final illness.

It was also important to consider the arrhythmia, and we thought that, in addition to the large doses of digitalis along with bed rest, that he was having for congestive failure, he should also receive quinidine, which ought to help to prevent a more serious disturbance of rhythm. Such a disorder of rhythm—namely, ventricular fibrillation—was one of the things that we thought of as a possible cause of his death. He was always afebrile. Nevertheless, if there were a rheumatic heart, whether aortic or mitral in type, there might have been a recurrent nodal myocardial involvement to explain the paroxysmal failure that came on. On the other hand, the acute physical strain when he ran for the train could have precipitated the illness—an unusual case, after which the present illness started.

DR. BREED: I was more impressed than Dr. White was with the association of the arrhythmia and what the patient called air hunger. I saw him more frequently and watched him with that in mind. The change in position with relief of the air hunger and return to bigeminy, as opposed to the grossly irregular rate when he was having the air hunger, was very impressive.

DR. WHITE: He was a nervous man and sensitive to the arrhythmia. That may have entered into the picture some.

DR. WILLIAMS: I should like to ask Dr. White a question. If you thought that this was mitral regurgitation, might the apparent failure have represented something else—such as pulmonary embolism?

DR. WHITE: We had seriously thought of it but did not enter it as a diagnosis. We also thought of coronary complications, but found no proof of them. The electrocardiogram was never that of coronary heart disease.

DR. WILLIAMS: Did you believe that the x-ray changes were enough to account for a diagnosis of cardiac failure on the basis of a lesion involving the mitral valve?

DR. WHITE: We did not have an x-ray examination after the heart began to fail.

DR. WILLIAMS: The note made on final physical examination states that the left border of dullness was 9 cm. to the left of the midsternal line, which does not suggest much enlargement.

DR. WHITE: The left border was difficult to find, but it seemed definitely beyond the normal position.

CLINICAL DIAGNOSES

Rheumatic heart disease, with mitral regurgitation.
Congestive heart failure.
Ventricular tachycardia or fibrillation, coronary occlusion or pulmonary embolus?

DR. WILLIAMS'S DIAGNOSES

Aortic stenosis (? rheumatic or calcareous).
Cardiac enlargement.
Congestive failure.
Pulmonary embolism?

ANATOMICAL DIAGNOSES

Rheumatic heart disease, with mitral regurgitation.
Cardiac hypertrophy.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At autopsy, the heart of this man weighed 550 gm., a little under twice what it should weigh. The enlargement was uniform throughout all chambers. The right ventricular wall, however, was not hypertrophied, measuring only 3 to 4 mm. The left ventricular wall was definitely hypertrophied, measuring 17 to 18 mm. There was no

coronary disease. The pathology was limited to the mitral valve, which was definitely fibrous (Fig. 1). Some of the chordae tendineae were thick and slightly shortened, but the circumference of the

This is a much rarer type of congestive failure and death in middle-aged and older men than is the due to aortic stenosis, the chances ordinarily being 10 to 1 in favor of aortic stenosis; it seemed to u

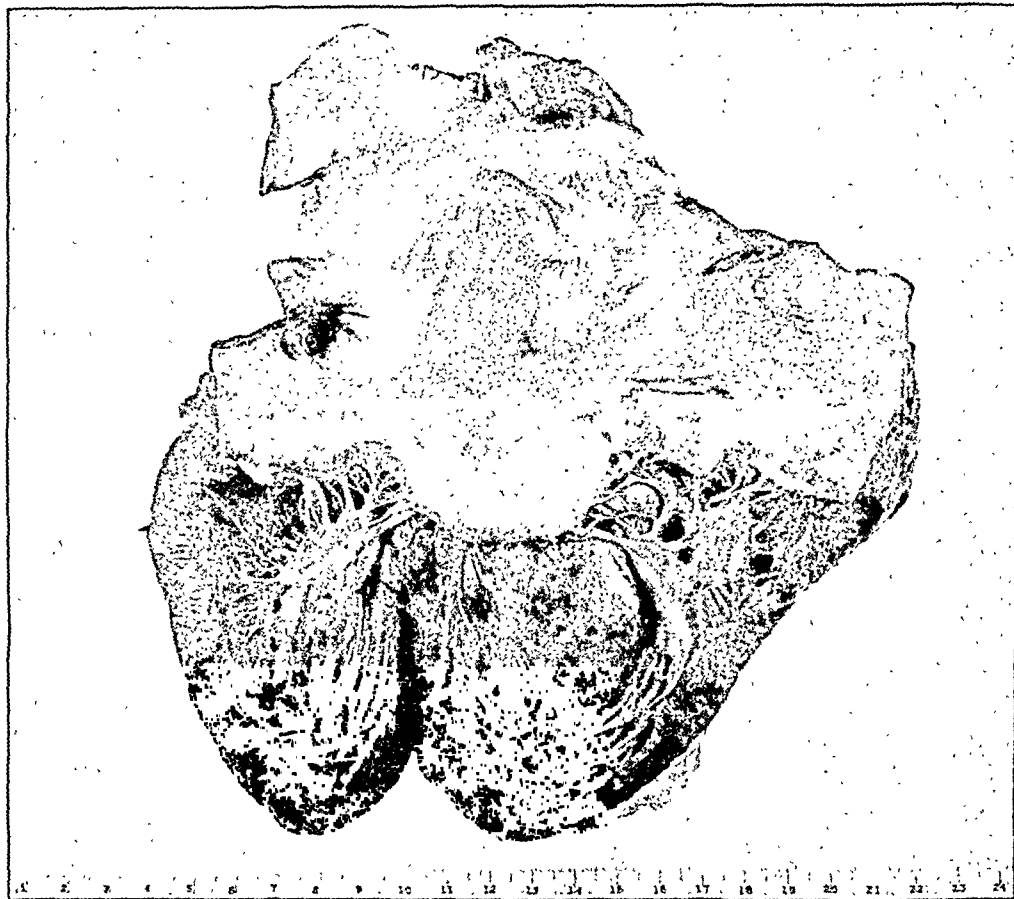


FIGURE 1. Photograph of Mitral Valve.

valve was markedly lengthened, measuring 15.2 cm. This was, then, a case of true mitral regurgitation—one of the few that we have had here as extensive as this. There was no disease of the aortic valve, and the myocardium showed no evident Aschoff nodules. The exact cause of death is still a mystery, but I suppose it was due to ventricular fibrillation or something of that nature.

DR. WHITE: That was our conclusion; he had probably not received enough quinidine to prevent fatal arrhythmia. He may have had ventricular tachycardia for a few seconds before the ventricles fibrillated.

at the time that the murmur and its transmission were significant.

DR. CASTLEMAN: At the time of autopsy there was little evidence of congestive failure. The liver showed only slight congestion.

DR. BREED: I was convinced before his death that the mild congestive failure from which he had suffered had been overcome and that, at the time of death, he was not suffering from congestive failure as such.

DR. WHITE: He was much better in that respect. He had improved quickly under treatment with digitalis and rest.

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ANNUAL MEETING

THE one hundred and sixty-third anniversary of the Massachusetts Medical Society will be held at the Hotel Statler, Boston, on May 22, 23 and 24; the program of the meeting appears elsewhere in this issue of the *Journal*.

According to the custom of the past two years, the annual meetings of the supervising censors and of the Council will be held in the late afternoon and evening, respectively, of Monday, May 22, the day before the opening of the regular sessions.

The scientific program set up by the Committee on Arrangements covers a wide variety of interesting and timely subjects that will be discussed by authoritative specialists.

The first morning will be devoted to a symposium on war injuries, including venereal disease, wound surgery, reconstructive surgery, the use of physical therapy, and psychiatric casualties and their treatment. Following the business portion of the annual meeting of the Society, the annual oration will be delivered by Dr. Joseph C. Aub. The afternoon session begins with a group of papers on miscellaneous topics and ends with the Shattuck Lecture, which will be given by Dr. Alfred Blalock, surgeon-in-chief at Johns Hopkins Hospital and professor of surgery, Johns Hopkins University School of Medicine, the title being "A Consideration of Certain Recent Advances in Surgery." The annual dinner of the Society will be held that evening; the president, Dr. Roger I. Lee, will preside, and the guest speakers will be the Honorable Leverett Saltonstall, Governor of Massachusetts, and Bill Cunningham, the well-known columnist of *The Boston Herald*.

The morning program for the second day comprises five papers on subjects of general interest and a symposium on gall-bladder disease, including the medical, surgical and radiologic aspects followed by a question-and-answer period. At noon, the sections will hold luncheon meetings, and at each a short talk is scheduled. The afternoon session will end with a panel discussion on the selection and use of new chemotherapeutic agents, under the chairmanship of Dr. Chester S. Keefer.

The scientific and technical exhibits, particularly the latter, will be more extensive than ever before. Pharmaceutical houses have made a tremendous contribution to the war effort, — in fact, one whose significance and value can never be appreciated until the ban of censorship has been lifted, — and what they have accomplished and are accomplishing deserves proper recognition by the medical profession, which can best be shown by visits to the booths of the commercial exhibitors.

Other attractions include the usual continuous motion-picture program on both days.

It is obvious that the Committee on Arrangements, composed of Dr. Gordon M. Morrison, chairman, and Drs. Roy J. Heffernan, Sidney C. Wiggin, Richard I. Smith and G. Guy Bailey, has put a large amount of time and thought in making the plans

for this meeting. Owing to the shortage of physicians, there is an increasing demand for efficient medical practice, and all members of the Society should welcome the opportunity of learning the most up-to-date methods from those who are qualified to discuss them. A good attendance seems assured.

JOURNAL OF NEUROSURGERY

THE publishing of a new journal devoted to neurosurgery adds to the firm foundation of this branch of medicine.¹ Neurological surgery developed largely in this country as the result of the stimulus given to it by Harvey Cushing, who began publishing papers on the subject as early as 1900 and continued up to the time of his death in 1939.² A society of neurosurgeons named in his honor has now established a journal with an editorial and advisory board that reflects the widespread interest in this subject. The chairman of the board is Dr. Gilbert Horrax, of Boston, long associated with Dr. Cushing at the Peter Bent Brigham Hospital. Other members are from Chile, Canada, England and Sweden. It is presumed that after the war representation from other parts of the world in which neurosurgery flourishes will appear on the editorial committees. The managing editor, Dr. Louise Eisenhardt, of New Haven, Connecticut, was also closely associated with Dr. Cushing for many years, and she collaborated with him in his final great volume reporting his surgical experience with meningiomas. Dr. Eisenhardt is head of the Brain Tumor Registry at the New Haven Hospital, an undertaking begun by Dr. Cushing, where many specimens from other clinics are examined yearly and compared with those already on file.

In the first number of the *Journal of Neurosurgery*, Dr. Horrax describes some of Harvey Cushing's contributions to the subject, reviewing the development of the technic of surgical exploration of the cranial contents by this master. Another paper deals with fibrin foams as hemostatic agents and with fibrin films in the repair of dural defects and in the prevention of meningocerebral adhesions; the authors are Dr. Franc D. Ingraham and Dr. Orville T. Bailey, of the Harvard Medical School

and the Children's Hospital. These and other contributions make the first number of this journal an important addition to medical literature. The illustrations are excellent, many of them being in color. This journal, therefore, is indeed a welcome addition to medical literature, and with the fine standards set up by the initial number the editor and her editorial advisers are open to sincere congratulations.

REFERENCES

1. *Journal of Neurosurgery*. Published bi-monthly for the Harvey Cushing Society. Charles C Thomas, 220 East Monroe St. Springfield, Illinois, 1944.
2. *A Bibliography of the Writings of Harvey Cushing*. Privately printed for the Harvey Cushing Society. Springfield, Illinois: Charles C Thomas, 1939

MASSACHUSETTS MEDICAL SOCIETY
DEATHS

DONALDSON — James F. Donaldson, M.D., of Middleton, died March 10. He was in his sixty-seventh year. Dr. Donaldson received his degree from Harvard Medical School in 1902. He was a member of the Massachusetts Medical Society, the American Medical Association, and the New England Pediatric Society. His widow and three sons survive.

HARVEY — Frank T. Harvey, M.D., of Milford, died February 1. He was in his seventy-eighth year. Dr. Harvey received his degree from the New York Medical College in 1893. He was a former member of the Massachusetts Medical Society, a member of the American Medical Association and an honorary member of the staff of the Milford Hospital.

JACQUES — J. Hector Jacques, M.D., of Fitchburg, died April 15. He was in his sixty-ninth year. Dr. Jacques received his degree from Harvard Medical School in 1910. He was a member of the Massachusetts Medical Society and the American Medical Association.

LOWNEY — John F. Lowney, M.D., of Fall River, died February 19. He was in his seventy-fifth year. Dr. Lowney received his degree from Tufts College Medical School in 1900. He was elected president of the Fall River Medical Society in 1907. He was a member of the Massachusetts Medical Society and the American Medical Association. His widow survives.

MAYHEW — Orland S. Mayhew, M.D., of Vineyard Haven, died February 26. He was in his sixty-seventh year. Dr. Mayhew received his degree from Harvard Medical School in 1901. He was examining physician of the Selective Service board and chief of staff of Martha's Vineyard Hospital. He was a member of the Massachusetts Medical Society, the American Medical Association and the Martha's Vineyard Medical Society. His widow, two daughters and a son survive.

MCAUSLAN — James L. McAuslan, M.D., of North Grafton, died March 22. He was in his seventieth year. Dr. McAuslan received his degree from Harvard Medical School in 1899. He was a member of the Massachusetts Medical Society, the American Medical Association, the American Psychiatric Association and the New England Psychiatry Association. His widow, two daughters and two sons survive.

PENNY—Mary M. Penny, M.D., of Saugus, died April 11. She was in her seventy-third year. Dr. Penny received her degree from Tufts College Medical School in 1910. She founded the preschool clinic in Saugus and was a member of the Massachusetts Medical Society, the American Medical Association and the Lynn Hospital Association. A daughter, a son, a brother and two grandsons survive.

VARNEY—Elton M. Varney, M.D., of Peabody, died April 11. He was in his sixty-sixth year. Dr. Varney received his degree from Bowdoin Medical School in 1903. He was a member of the Massachusetts Medical Society and the American Medical Association. His widow survives.

WINSLOW—George F. Winslow, M.D., of Hyde Park, died April 17. He was in his sixty-eighth year. Dr. Winslow received his degree from Harvard Medical School in 1901. After serving his internship at Carney Hospital he entered practice in Hyde Park in 1903. He was an attending physician for the Boston schools and for several industrial plants in Hyde Park. Dr. Winslow was a member of the Massachusetts Medical Society, the American Medical Association and the Society of Examining Physicians of Boston. His widow, a daughter, a brother and two grandchildren survive.

WAR ACTIVITIES

CIVILIAN DEFENSE

AUXILIARY EMERGENCY MEDICAL DEPOTS

The following are the requirements for retail druggists whose stores qualify as auxiliary emergency medical depots as approved by the Committee on the Massachusetts

1. The drugstore shall be approved by the committee as a suitable store for a depot.
2. The drugstore shall always have on hand suitable medical supplies to care for a minimum of fifty persons who may be in need of medical supplies in time of emergency or disaster.
3. The owner and his employees shall be subject to call at any hour to provide these medical supplies in the event of emergency or disaster.
4. The owner shall sign an agreement that he will make available the necessary medical supplies to the Civilian Defense or Red Cross authorities when called on in the event of an emergency or disaster.
5. The owner shall agree to make available these supplies whether the emergency or disaster arises out of the war or from any other accident or disaster to which the Civilian Defense or Red Cross authorities may respond.
6. The owner shall comply with all the requirements and regulations promulgated or issued by the Medical Division of the Massachusetts Committee on Public Safety.
7. The owner and his employees shall take orders from the chief medical officer of the community in which his store is located or from such other officer or representatives as the Medical Division of the Massachusetts Committee on Public Safety or the local chief medical officer shall designate.
8. The owner and his employees shall hold themselves in readiness to co-operate and assist all duly authorized representatives of the Massachusetts Committee on Public Safety in time of emergency or disaster.
9. The owner shall place in his front store window the insignia of the Auxiliary Emergency Medical Depot in accordance with the directions of the Committee on Auxiliary Emergency Medical Depots and shall not

use any other insignia or form of advertising except as approved by the Committee on Auxiliary Emergency Medical Depots.

10. The owner shall surrender to the Committee on Auxiliary Emergency Depots his insignia and Civilian Defense button if in the opinion of the committee it be determined that his store is no longer a proper place to be designated as a depot.
11. The owner shall attend all meetings to which he may be invited by the local medical committee of the Massachusetts Committee on Public Safety.
12. The owner shall agree that all medical supplies furnished to the Civilian Defense or Red Cross authorities in time of an emergency or disaster shall be without cost to said authorities and shall be his contribution to the welfare of the community and the Commonwealth.

CORRESPONDENCE

PROCUREMENT AND ASSIGNMENT OF NURSES

To the Editor The Procurement and Assignment Service for Nurses has two objectives to procure the necessary nurses for the military services with due consideration for civilian needs and to bring about an equitable redistribution of nurses to maintain essential civilian nursing services.

Enlistment of nurses in the military service is voluntary but no nurse may be accepted for military service until given a I-A classification by a committee of the Procurement and Assignment Service. By reviewing the positions of all eligible nurses the committees are making as fair a determination as possible of those best able to be declared available for military service while they are deferring those who are most essential to civilian needs.

To secure the numbers needed by the Army and Navy, a certain number of young eligible nurses will have to go from the private-duty field and general hospital public health and industrial nursing services as well as from doctors' offices if they are doing non-nursing work or work that can be taken over without difficulty by a nurse ineligible for military service.

With the very acute shortage of physicians the essentiality of the nurse assistant to the private physician or surgeon is recognized. In order to meet our obligations and still protect all the essential civilian services however, we ask the co-operation of the doctors in two ways:

1. To give the Committee of the Procurement and Assignment Service the office of nursing so as to
2. To hold nurses as nursing duties and not to employ young graduates who are our most promising source of recruits for the military service.

The Army quota for 1944 has been reduced, the Navy quota remains the same. Massachusetts is asked to procure 434 nurses by July 1. The needs after that date are not known.

The response of nurses is excellent and we think that we shall be not far below our quota. We hope that we can also protect the places where the strains are most acute in civilian service owing to nursing shortage. To do so the support of the physicians is needed.

MASSACHUSETTS COMMITTEE FOR PROCUREMENT AND ASSIGNMENT OF NURSES

Katharine F. Peirce, *Chairman*
Mrs. Lloyd D. Bracer
Dorothy J. Carter
Nathaniel P. Laxon, M.D.
Bessie P. Hanson
Ilanche P. Harriman
Katharine P. McGabe
Dwight O'Hara, M.D.
Helen O. Potter
Iva S. Waldron
Margorie B. Davis, *ex officio*
Margaret Dieter, *ex officio*
Helene G. Lee, *ex officio*

OFFICERS OF THE MASSACHUSETTS MEDICAL SOCIETY, 1943-1944



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Bachrach

DR. ELIOT HUBBARD, JR., *Treasurer*

PROGRAM OF THE ONE HUNDRED AND SIXTY-THIRD ANNIVERSARY OF THE MASSACHUSETTS MEDICAL SOCIETY

Monday, Tuesday and Wednesday, May 22, 23 and 24, Hotel Statler, Boston

The Registration Desk will be located on the Mezzanine Floor, and all who attend the meeting are requested to register.

Owing to the lack of personnel and food supplies, the Hotel Statler must be informed concerning the number of members who will attend the various luncheons and dinners. Attendance is not limited, but tickets *must* be obtained in advance. It is doubtful whether any tickets will be available at the time of the meeting.

MONDAY EVENING, MAY 22

Annual Meeting of the Council of the Massachusetts Medical Society

- 5:00 Supervising Censors' Meeting (PARLOR D).
6:00 Cotting Supper (PARLORS A AND B).
7:00 Council — Annual Meeting (GEORGIAN ROOM).

TUESDAY MORNING, MAY 23

First General Session

GEORGIAN ROOM

Dr. George L. Schadt, *Chairman*
Dr. G. Lynde Gately, *Co-chairman*

Symposium on War Injuries

- 9:00 *Venereal Disease as a War Injury.* Dr. Oscar F. Cox, Boston. Associate professor of medicine, Boston University School of Medicine; clinical professor of urology, Tufts College Medical School; director, Division of Genitoinfectious Diseases, Massachusetts Memorial Hospitals; member, Subcommittee on Venereal Diseases, National Research Council.
- 9:20 *Surgical Experiences with Wounds in the Papua Campaign.* Colonel Augustus Thorndike, M.C., A.U.S., Washington, D. C.
- 9:40 *Reconstructive Surgery.* Dr. Philip D. Wilson, New York. Surgeon-in-chief, Hospital for Special Surgery, New York; clinical professor of orthopedic surgery, Columbia University College of Physicians and Surgeons.
- 10:00 *Physical Therapy: Its relation to war injuries.* Dr. Kristian G. Hansson, New York. Director of physical therapy, Hospital for Special Surgery and New York Hospital.
- 10:20 *Psychiatric Casualties of the War, and Their Treatment.* Dr. Winfred Overholser, Washington, D. C. Superintendent, Saint Elizabeth's Hospital, Washington, D. C.; professor of psychiatry, Washington University School of Medicine; Chairman, Committee on Neuropsychiatry, Research Council.

11:00 Annual Meeting of the Massachusetts Medical Society

GEORGIAN ROOM

Annual Oration (following annual meeting): *The Toxic Factors in Traumatic Shock.* Dr. Joseph C. Aub, Boston. Professor of research medicine, Harvard Medical School; physician, Massachusetts General Hospital; director, Collis P. Huntington Memorial Hospital, Massachusetts General Hospital.

Annual Luncheon (PARLORS A, B, and C): tickets MUST be procured in advance of the meeting.

TUESDAY AFTERNOON, MAY 23

Second General Session

GEORGIAN ROOM

Dr. Dwight O'Hara, *Chairman*
Dr. Clifton T. Perkins, *Co-chairman*

- 2:00 *The Practitioner, the Surgeon and Endometriosis.* Dr. John Fallon, Worcester. Surgeon, Fallon Clinic.
- 2:20 *Some Practical Aspects of Female Genital Bleeding.* Dr. Richard W. Te Linde, Baltimore, Maryland. Professor of gynecology, Johns Hopkins University School of Medicine; chief gynecologist, Johns Hopkins Hospital.
- 2:40 *A Comparison of Results in Immediate and Delayed Treatment of Injured Nerves of the Forearm and Hand.* Dr. William E. Browne, Boston. Surgeon-in-chief, Second Surgical Service, Carney Hospital; clinical professor of surgery, Tufts College Medical School.
- 3:00 *Typhus.* Rear Admiral C. S. Stephenson (MC), U.S.N., Washington, D. C.
- 3:20 *Tropical Diseases of the Skin.* Dr. Howard Fox, New York. Professor of dermatology and syphilology, emeritus, New York University School of Medicine.
- 3:40 *The Study of a Patient from the Psychosomatic Standpoint.* Dr. Kenneth J. Tillotson, Belmont. Psychiatrist-in-chief, McLean Hospital, Waverley, Massachusetts.
- 4:00 *The Shattuck Lecture. A Consideration of Certain Recent Advances in Surgery.* Dr. Alfred Blalock, Baltimore, Maryland. Surgeon-in-chief, Johns Hopkins Hospital; professor of surgery, Johns Hopkins University School of Medicine.

TUESDAY EVENING, MAY 23

X Annual Dinner of the Massachusetts Medical Society

GEORGIAN ROOM

tickets for the dinner MUST be procured in advance.

Residing: Dr. Roger I. Lee, president, Massachusetts Medical Society.

1st Speakers:

The Honorable Leverett Saltonstall, Governor of Massachusetts.

William (Bill) Cunningham, of *The Boston Herald*.

WEDNESDAY MORNING, MAY 24

Third General Session

GEORGIAN ROOM

Dr. Charles F. Wilinsky, *Chairman*

Dr. Leroy E. Parkins, *Co-chairman*

1) *Advances in Inhalation Therapy.* Dr. Maurice S. Segal, Boston. Assistant professor of medicine, Tufts College Medical School.

0) *The Apprehension of Silent and Masquerading Diseases of the Chest.* Dr. Norman J. Wilson, Boston. Assistant in surgery, New England Deaconess Hospital.

2) *Practical Consideration in the Diagnosis and Treatment of Infantile Paralysis.* Dr. William T. Green, Boston. Director of clinics, Harvard Infantile Commission.

3) *The Rehabilitation of Returned Veterans in Industry.* Dr. Frederic N. Manley, Quincy. Chief surgeon, Bethlehem Steel Corporation, Shipbuilding Division, Boston Area; associate professor of industrial medicine, Tufts College Medical School.

4) *Postwar Planning in Anesthesiology.* Dr. Henry S. Ruth, Philadelphia. Professor and chief of the Section of Anesthesiology, Hahnemann Medical College and Hospital, Philadelphia.

Symposium on Gall-Bladder Disease

5) *Medical View of Gall-Bladder Disease.* Dr. Walter C. Alvarez, Rochester, Minnesota. Professor of medicine, University of Minnesota (Mayo Foundation); consultant, Division of Medicine, Mayo Clinic.

6) *Surgical Aspects of Gall-Bladder Disease.* Dr. Howard M. Clute, Boston. Professor of surgery, Boston University School of Medicine; surgeon-in-chief, Massachusetts Memorial Hospitals; surgeon, New England Baptist Hospital.

7) *Radiologic Aspects of Gall-Bladder Disease.* Dr. Merrill C. Sosman, Boston. Roentgenologist, Peter Bent Brigham Hospital; clinical professor of roentgenology, Harvard Medical School.

8) *Question-and-Answer Period on Gall-Bladder Disease*

WEDNESDAY NOON, MAY 24

Section Meetings and Luncheons

12:00 m.-2:00 p.m.

Tickets for the luncheon MUST be procured in advance.

Section of Medicine

PARLOR B, HOTEL STATLER

Dr. George D. Henderson, Holyoke, *Chairman*

Dr. Albert A. Hornor, Boston, *Secretary*

Abdominal Pain. Dr. Walter C. Alvarez, Rochester, Minnesota. Professor of medicine, University of Minnesota; consultant, Division of Medicine, Mayo Clinic.

Section of Surgery

PARLOR C, HOTEL STATLER

Dr. Howard M. Clute, Boston, *Chairman*

Dr. Charles F. Twomey, East Lynn, *Secretary*

How Shall We Provide Postgraduate Training in Surgery for Men at Present Serving in the Armed Forces? Dr. Allen O. Whipple, New York. Professor of surgery, Columbia University College of Physicians and Surgeons; director of the Surgical Service, Presbyterian Hospital, New York.

Section of Pediatrics

THE JUNIOR LEAGUE, ZERO MARLBOROUGH STREET

Dr. Leroy T. Stokes, Haverhill, *Chairman*

Dr. Gerald N. Hoeftel, Cambridge and Boston, *Secretary*

Therapy of Anemias in Childhood. Dr. Louis K. Diamond, Boston. Assistant professor of pediatrics, Harvard Medical School; visiting physician, Children's and Infants' hospitals.

Section of Obstetrics and Gynecology

PARLOR A, HOTEL STATLER

Dr. Christopher J. Duncan, Brookline, *Chairman*

Dr. F. G. Edgelow, Springfield, *Vice-chairman*

Dr. George Van S. Smith, Brookline, *Secretary*

Dysmenorrhea: Its cause and treatment. Dr. Frank A. Pemberton, Boston, Dr. George Van S. Smith, Boston, and Dr. Louis E. Phaneuf, Boston.

Section of Radiology

FOURTH FLOOR, HOTEL STATLER

Dr. Stanley A. Wilson, Salem, *Chairman*

Dr. George Levene, Chestnut Hill and Boston, *Secretary*

Uterine Bleeding. Dr. Joe V. Meigs, Boston.

Section of Physiotherapy

FOURTH FLOOR, HOTEL STATLER

Dr. Wilmot L. Marden, Boston and Lynn, *Chairman*

Dr. Howard Moore, Newton and Boston, *Secretary*

Occupational Therapy for War Wounded and Physical Medicine in Army Practice. Captain Sidney Licht, Chief physical therapist, Lovell

Section of Dermatology and Syphilology

HANCOCK ROOM, HOTEL STATLER

Dr. John G. Downing, Newton and Boston, *Chairman*Dr. G. Marshall Crawford, Lincoln and Brookline, *Secretary**Pinta.* Dr. Howard Fox, New York. Professor of dermatology and syphilology, emeritus, New York University College of Medicine.**MASSACHUSETTS MEMBERS OF THE NEW ENGLAND SOCIETY OF ANESTHESIOLOGY**

PARLORS D AND E, HOTEL STATLER

Anesthesia: A general discussion. Dr. Henry S. Ruth, Philadelphia. Professor and chief of the Section of Anesthesiology, Hahnemann Medical College and Hospital, Philadelphia.

WEDNESDAY AFTERNOON, MAY 24

Fourth General Session

GEORGIAN ROOM

Dr. Daniel B. Reardon, *Chairman*Dr. Vlado A. Getting, *Co-chairman*2:00 *The Goal of an Eye-Hygiene Program for School Children.* Dr. James J. Regan, Boston. Ophthalmic surgeon-in-chief, Boston City Hospital; assistant professor of ophthalmology, Tufts College Medical School.2:20 *Differential Diagnosis of Weakness and Fatigue.* Dr. Frank N. Allan, Boston. Co-director, Department of Internal Medicine, Lahey Clinic.2:40 *The Prevention of Pulmonary Embolism.* Dr. Charles A. Robinson, Boston. Junior visiting surgeon, First Surgical Service, Carney Hospital; chief of Varicose Vein Clinic, Carney Hospital.3:00 *Clinical Importance of the Rh Blood Type.* Dr. Louis K. Diamond, Boston. Assistant professor of pediatrics, Harvard Medical School; visiting physician, Children's and Infants' hospitals.3:20 *Review of McMurray Osteotomies for Ununited Hip Fractures.* Dr. Otto J. Hermann, Boston. Clinical professor of surgery, Tufts College Medical School; associate in surgery, Harvard Medical School; surgeon-in-chief, Bone and Joint Service, Boston City Hospital.3:40 *Nutrition in Postwar Rehabilitation.* Dr. Fredrick J. Stare, Boston. Assistant professor of nutrition, Harvard Medical School and School of Public Health; junior associate in medicine, Peter Bent Brigham Hospital.4:00 *Panel Discussion: The selection and use of the newer drugs.* Dr. Chester S. Keefer, *Chairman*. Director, Evans Memorial Hospital; physician-in-chief, Massachusetts Memorial Hospitals; Wade Professor of Medicine, Boston University School of Medicine.*Discussers:*

Dr. Charles A. Janeway. Assistant professor pediatrics, Harvard Medical School and School of Public Health; visiting physician, Children's and Infants' hospitals.

Dr. Maxwell Finland. Assistant professor of medicine, Harvard Medical School; associate physician, Thorndike Memorial Laboratory; chief, Fourth (Harvard) Medical Service, Boston City Hospital.

Dr. Donald G. Anderson. Research fellow in medicine, Evans Memorial Hospital; instructor in medicine, Boston University School of Medicine.

Scientific Exhibits**BALLROOM ASSEMBLY**Booth
S-13-16*Anesthesia.* Massachusetts members of the New England Society of Anesthesiology. Exhibitors: Boston City Hospital, Massachusetts General Hospital, Massachusetts Memorial Hospitals and Lahey Clinic (Dr. U. Eversole, Dr. L. V. Hand and Dr. M. Nicholson).

S-17

Weakness and Fatigue. Lahey Clinic. Exhibitor: Dr. Frank N. Allan.

S-18

Occupational Disease Prevention. Massachusetts Division of Occupational Hygiene.

S-19-20-21

Malaria Control. Massachusetts Department of Public Health and Massachusetts Reclamation Board.

S-22

Veneral Disease Control. Massachusetts Department of Public Health.

S-23

Fractures. Massachusetts Committee on Fractures and Trauma, American College of Surgeons. Demonstration of first aid members of the American Red Cross Metropolitan Chapter, Boston and Newton chapters.

S-24

Modern Pharmacy. Massachusetts State Pharmaceutical Association.

S-25-26

The Health Department Serves the Physician. The Health Department, City of Boston.

S-27

Blood for Victory. Blood Donor Centre, Boston Metropolitan Chapter, American Red Cross.

S-28

Industrial Dermatitis. The Department of Dermatology, Boston University School of Medicine. Exhibitor: Dr. F. Ronchese.

S-29

Absenteeism. The Committee on Industrial Health. Exhibitor: Dr. Daniel L. Lynch.

S-30

Cancer of the Larynx. Dr. L. A. Schall.

S-31

X-ray Finds Tuberculosis Early — Listen! Finds It Late. Massachusetts Tuberculosis League.

S-32

The Answer to Socialized Medicine. The Blue Cross and the Blue Shield.

MEZZANINE

- (1) *Penicillin and Results of Therapy with this Agent.* (2) *Model of Rehabilitation Workshop, and Management of Battle Casualties.* (3) *Tropical Diseases: Its problems here and in the South Pacific.* (4) *The Control of Streptococcal Infections.* Medical departments, United States Army, First Service Command, and the United States Navy, First Naval District.

Motion Picture Program

LOWER LOBBY

Tuesday, May 23

- 9:45 *Inguinal Hernia.*
 0:00 *Surgical Pathology of the Appendix.*
 0:15 *Surgical Pathology of the Breast.*
 0:45 *Cancer of the Female Breast.*
 1:15 *Treatment of Normal Breach Presentation.*
 1:40 *Continuous Caudal Analgesia.*
 2:00 *Transverse Cervical Cesarean Section.*
 2:40 *Combined Abdominoperineal Resection of the Rectum (Miles Technic).*
 3:00 *First-Stage Thoracoplasty for Pulmonary Tuberculosis.*
 3:45 *Second-Stage Thoracoplasty for Pulmonary Tuberculosis.*
 3:50 *Nephrectomy for Tuberculosis of the Kidney.*
 4:00 *Fusion of Lumbosacral Joint and Hemilaminectomy for Removal of Herniated Disk.*
 4:20 *Surgical Anatomy of the Hand.*
 4:40 *Correction of Nasal Deformities.*

Wednesday, May 24

- 0:00 *Subtotal Thyroidectomy for Primary Hyperthyroidism.*
 0:15 *Open Reduction of Fracture of Neck of Femur.*
 0:30 *Use of the Miller-Abbott Tube.*
 1:00 *Skin Grafting of War Wounds.*
 1:30 *Treatment of War Burns of the Hand.*
 1:50 *Immunization Against Infectious Diseases.*
 2:30 *Subtotal Gastrectomy for Perforating Duodenal Ulcer.*
 2:45 *Ileostomy for Ulcerative Colitis.*
 3:00 *Hemorrhoids and a Method of Hemorrhoidectomy.*
 3:30 *Abdominal Complete Hysterectomy for Fibroids.*
 4:00 *Vaginal Repair of Cystocele and Rectocele.*
 4:15 *Radical Operation for Carcinoma of Prostate.*
 4:30 *Repair of Burn Contractures of the Neck.*
 4:50 *Reconstruction of Nose.*

Technical Exhibitors

booths without letters are in the Ballroom; those
 ed by "S," in the Ballroom Assembly; and those
 ed by "M," in the Mezzanine.

	Booth No.
Laboratories	56
A Company	22
can Hospital Supply Corporation	M-15
McKenna and Harrison	19
Laboratories	5
oods, Incorporated	M-5
ber-Knoll Corporation	34
Bischoff Company	M-9
orden Company	28
and Company	3-4

Buffington's, Incorporated	39
Burroughs Wellcome and Company, Incorporated	23
Cambridge Instrument Company	M-13
Camel Cigarettes	11-12
S. H. Camp and Company	M-6 & 7
Carnation Company	S-1
Children Incorporated	9
Ciba Pharmaceutical Products, Incorporated	44
Coca-Cola Company	S-7-8
Crosbie-Macdonald	46
Davies, Rose and Company, Limited	40
Denver Chemical Company	M-8
De Vilbiss Company	M-4
Doho Chemical Corporation	S-10
Effervescent Products Company	S-11
J. H. Emerson Company	S-12
C. B. Fleet Company	45
Gerber Products Company	13
J. E. Hanger, Incorporated	35
Hanovia Chemical and Manufacturing Company	51
H. J. Heinz Company	27
Hoffmann-La Roche, Incorporated	29
Horlick's Malted Milk Corporation	43
Hudnut Institute for Dermatological Research	1-2
Hynson, Westcott and Dunning, Incorporated	17
Jones Metabolism Equipment Company	33
Kelley-Koett Manufacturing Company, Incorporated	7
Kellogg Company	42
Lederle Laboratories, Incorporated	38
Libby, McNeill and Libby	20
Eli Lilly and Company	8
M and R Dietetic Laboratories, Incorporated	16
E. F. Mahady Company	14-15
Mead Johnson and Company	53
Medical Protective Company	21
Mellin's Food Company	31
Mennen Company	M-14
Merck and Company, Incorporated	52
National Drug Company	M-17
Nutritional Research Laboratories	M-11
Parke, Davis and Company	M-10
E. L. Patch Company	S-2
Pet Milk Sales Corporation	25
Philip Morris and Company Limited, Incorporated	S-9
Pitman-Moore Company	S-4
Riedel-de Haen, Incorporated	54
Sandoz Chemical Works, Incorporated	49
Schering Corporation	41
G. D. Searle and Company	24
Sharp and Dohme, Incorporated	50
Singer Sewing Machine Company	S-6
Smith, Kline and French Laboratories	32
Spencer, Incorporated	S-3
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Standard X-Ray Sales Corporation	10
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Teca Corporation	M-18
William R. Warner and Company, Incorporated	5-6
White Laboratories, Incorporated	36-37
Winthrop Chemical Company, Incorporated	55
Wyeth, Incorporated	M-1-2-3
F. E. Young and Company	26
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AMERICAN COLLEGE OF SURGEONS

A meeting of the Regional Fracture Committee of Massachusetts of the American College of Surgeons will be held in Parlor C of the Hotel Statler at 2:00 p.m., Wednesday, May 24.

MASSACHUSETTS MEDICO-LEGAL SOCIETY

A meeting of the Massachusetts Medico-Legal Society will be held on the fourth floor of the Hotel Statler at 2:00 p.m., Tuesday, May 23 (the room number can be obtained at the Information Desk, Hotel Statler).

BOOK REVIEWS

Proteins, Amino Acids and Peptides as Ions and Dipolar Ions. By Edwin J. Cohn, Ph.D., and John T. Edsall, M.D. 8°, cloth, 686 pp., with tables and charts. New York: Reinhold Publishing Corporation, 1943. \$13.50.

The authors attest, in their preface, the significance of the purely physicochemical work of Debye and Hückel and of Bjerrum in the development of knowledge of protein chemistry since 1923. The book as a whole summarizes the experimental and mathematical approaches whereby the size and shape of protein molecules have been determined. In gaining this end, the authors include full discussions of many related physical properties of proteins, amino acids and other ion-dipoles. Such properties include viscosity, solubility, distribution of charges and the like. A chapter on the amino acid composition of proteins is included. Although full consideration is given to all significant advances in this particular field, the book is of particular value for its exposition of certain special methods, some of which have reached their fullest development in the authors' laboratories; such methods include measurements of dipole moments and of double refraction of flow. It appears to the reviewer to be the most outstanding monograph on this particular subject since the publication of Jacques Loeb's classic. The style is scholarly and richly mathematical, with no attempt at popularization and with no discussion of the many possible medical and technological applications of the material presented.

An Introduction to Clinical Perimetry. By H. M. Traquair, M.D., F.R.C.S. (Edin.). With a foreword by Norman M. Dott, M.B., Ch.B., F.R.C.S. (Edin.). Fourth edition, revised and enlarged. 8°, cloth, 332 pp., with 245 illustrations and 3 coloured plates. London: Henry Kimpton, 1942. \$6.50.

Traquair's fourth edition constitutes an authoritative and indispensable guide to ophthalmologists, neurologists and neurosurgeons for an understanding, both qualitative and quantitative, of the visuosensory mechanism, and thus for adequate localization and follow-up of lesions affecting the visual pathways from the retina to the visual cortex.

Excellent clinical judgment, which can grow only from extensive and discerning experience, speaks out from each page of the text. Lucid writing, well-chosen illustrations, nearly five hundred references to the literature, and an ample index of authors and titles combine to make this volume most useful to the practitioner working in the overlapping fields of ophthalmology and neurology. Indeed, the best interests of the patient are not served unless the practitioner understands and applies the principles that are so well outlined in this text, and applies them early in the study of the patient.

In the past, perimetric and tangent screen examinations have too often been postponed until gross defects have appeared in the visual fields. Now, early localization of lesions of the visuosensory pathways should be the aim of every practitioner, either through acquiring skill in perimetry on his own account or through the addition of a skilled perimetrist to his staff. Adequate perimetry requires time, patience, understanding and intelligent co-operation on the part of the patient, a bilateral game that permits no "short-cuts."

This book clearly points the way to more effective practice. Let it be hoped that every first-class ophthalmologist and neurologist will avail himself of this help.

A Handbook of Psychiatry. By P. M. Lichtenstein, M.D., LL.B., and S. M. Small, M.D. 8°, cloth, 330 pp. New York: W. W. Norton & Company, Inc., 1943. \$3.50.

This book is rather unusual. It is excellently written and covers the field of psychiatry, with up-to-date references to the literature. The aim of the book is not to provide a text for the teaching of psychiatry or for a book to supply the needs of the general practitioner. It is intended for those who have charge of psychiatric cases in hospitals, particularly nurses and social workers, and also for the representatives of the law who have to deal with mental problems regarding commitment in the commission of crime. In the reviewer's opinion, this is a sound book and should be extremely helpful to any intelligent layman, such as an officer of the law who had to deal with psychiatric problems.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Modern Management of Colitis. By J. Arnold Bagen, M.D., chief of the Section on Intestinal Diseases, Division of Medicine, Mayo Clinic, and associate professor of medicine, Mayo Foundation, Rochester, Minnesota. 8°, cloth, 322 pp., with 148 illustrations. Springfield, Illinois: Charles C Thomas, 1943. \$7.00.

This special monograph is based mainly on the author's observations and experiments at the Mayo Clinic. The classification of the types of ulcerative colitis has been made and recorded in this volume.

The Johns Hopkins Hospital and The Johns Hopkins University School of Medicine: A chronicle. Volume I. *Early years, 1867-1893.* By Alan M. Chesney, M.D., associate professor of medicine and dean of the medical faculty, Johns Hopkins University School of Medicine. With a foreword by William H. Howell, Ph.D. 8°, cloth, 318 pp., with 36 illustrations and frontispiece. Baltimore: The Johns Hopkins Press, 1943. \$3.00.

This history brings out clearly the relations between the school and the hospital that have existed from the beginnings of these two institutions. It covers the period when Drs. Welch, Osler, Halstead and Kelly were active in the hospital.

Psychological Medicine: A short introduction to psychiatry. With an appendix, "War-Time Psychiatry." By Desmond Curran, M.B., F.R.C.P., D.P.M., psychiatrist and lecturer in psychological medicine, St. George's Hospital, and honorary psychiatrist to the Maida Vale Hospital for Nervous Diseases, London; and Eric Guttman, M.D., L.R.C.P.Ed., neuropsychiatric specialist, Emergency Medical Service. With a foreword by J. J. Conybeare, D.M. (Oxon), physician to Guy's Hospital, London. 8°, cloth, 188 pp., with 21 illustrations. Baltimore: The Williams and Wilkins Company, 1943. \$3.50.

This short manual on psychiatry includes the experience of the present war period that has brought to light great numbers of psychiatric patients in the services and on the home front. The appendix on wartime psychiatry should be of great value to medical officers in the armed services.

NOTICES

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Friday, May 12, at 8:30 p.m. Dr. Joseph E. F. Riseman will show a motion picture entitled "Angina Pectoris," in color and sound. A discussion by Dr. Samuel Levine will follow.

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MENINGOENCEPHALITIS IN LYMPHOGRANULOMA VENEREUM*

A Report of Two Cases

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WASHINGTON, D.C.

LYMPHOGRANULOMA VENEREUM has been extensively studied since 1913, when first in the disease received added impetus from the report of Durand, Nicolas and Favre.¹ In the recent years evidence has accumulated tending to emphasize the concept that this virus infection is not a localized disease but is in reality a systemic infection.²⁻⁶ Besides the more frequent involvement of the genitals and regional lymph nodes, with or without rectal stricture as a sequela, in Rooyen² has listed the following ways in which lymphogranuloma venereum may manifest itself: involvement of the throat, with inflammation of the tonsils, ulceration or angina; fever, with headache and other pyrexial disturbances; skin rashes; various forms of articular involvement; generalized involvement of the lymph nodes, with splenomegaly and hepatomegaly; granulomatous conjunctivitis; epididymitis; and meningoencephalitis. Harrop et al.^{4,5} have extended the clinical knowledge of this virus disease by a description of 3 cases occurring in laboratory workers. In these patients the infection was associated with a septic type of fever, chills and sweats, articular rheumatism, headache and, in 2 cases, cervical lymphadenitis. In the last-named cases, the authors were of the opinion that the patients were infected via the upper respiratory tract, and stated that lymphogranuloma venereum can occur as an acute infection without apparent localization and tissue reaction at the point of invasion.

Of increasing interest has been the demonstration of involvement of the central nervous system by lymphogranuloma venereum. Findlay⁷ demonstrated changes characteristic of meningoencephalitis in monkeys, mice, guinea pigs, rabbits and dogs following intracerebral inoculation with the virus. Although the occurrence of severe headaches in human cases was long known, its importance was not sufficiently stressed until von Haam and Aunoy⁸ published their studies in 1936. They isolated the virus from the spinal fluid of 2 patients dur-

ing the acute stage of infection, thereby incriminating the agent when the cerebral manifestations consisted mainly of headache. During the same year, Rajam⁹ reported a clinically diagnosed case of lymphogranuloma venereum in which there had been surgical interference with the inguinal buboes. This was followed by an acute exacerbation of the illness, with manifestations of severe meningoencephalitis and death. Sabin and Aring⁶ recently published evidence that more definitely established this agent as a cause of severe meningoencephalitis in man. On two occasions they isolated the virus from the spinal fluid of a patient showing marked cerebral changes. The virus was also obtained from an inguinal lymph node six weeks after the onset of the acute phase of illness and from a penile wart. Further proof of the etiologic relation of the virus to the illness encountered was found in complement-fixation studies.

In the present paper additional evidence is submitted that lymphogranuloma venereum may be a cause of acute meningoencephalitis. The first case described offers several other clinical features of interest. These include the isolation of the virus from an inguinal lymph node some five months after the onset of illness, the spinal block encountered, the striking spinal-fluid findings and the results of Frei tests and complement-fixation tests with a variety of antigens. In addition, the isolation of the virus and the experiments leading to its identification are detailed.

A second case of meningoencephalitis probably due to lymphogranuloma venereum is briefly described.

CASE REPORTS

CASE 1. L. B. A., a 24-year-old Negro private, was admitted to the Sta. . . . The date of onset of illness . . . recovered to be questioned, however, the patient stated that he had been in excellent health until the latter part of September, when he first noted the formation of a "knot" about the size of an almond in the right inguinal region. This was followed in a few days by the appearance of a grayish, watery urethral discharge without associated burning or irritation. The

*From the Division of Virus and Rickettsial Diseases, Army Medical School, Washington, D.C.

patient's last exposure to venereal disease had occurred 4 weeks prior to the appearance of the discharge, with previous exposures at 2-week intervals to the same person.

At that time the patient was transferred from Camp Gordon, Georgia, to Indiantown Gap and, while en route, experienced chilly sensations, weakness and severe bi-frontal and occipital headache. After arriving at his new post, he went to the Dispensary regularly because of the severe headache. Since his temperature was found to be mildly elevated, he was given analgesics, with little relief. On his calling attention to the urethral discharge, he was given sulfonamide tablets, of which he took 6 daily for one week. This lessened the amount of urethral discharge but did not stop it.

On October 10, still troubled with weakness, chills, feverishness and severe headaches, the patient went A.W.O.L. to visit his home in Texas. There he continued to be ill and was advised by a physician to return to camp. While on the train

There were 541 white cells per cubic millimeter, with 20 per cent polymorphonuclear leukocytes and 80 per cent lymphocytes. The globulin reaction was markedly positive.

Mental clearing continued, with a gradual improvement of the memory. The patient had no recollection of events for 5 days beginning on October 24. He complained of blurring of vision and diplopia and persistent headache. By November 6, the stiffness of the neck had decreased and a lumbar puncture again gave signs of block. Marked weakness and pains in the extremities were prominent complaints. Although there was slow, steady general improvement, the patient was transferred on December 12 to the Walter Reed General Hospital in Washington, D. C., because of the persisting spinal block.

At that time the patient did not appear very ill, was well oriented and displayed no mental aberrations. He complained of generalized weakness and headaches. Examination revealed weakness of all four extremities, more marked in the proximal musculature. He was unable to lift his arms and

TABLE 1. *Spinal-Fluid Findings in Case 1.*

DATE	PRESSURE				AMOUNT REMOVED	FINAL PRESSURE	COLOR	CELL COUNT	GLOBULIN REACTION	TOTAL PROTEIN	COLLOIDAL GOLD CURVE
	INITIAL	AFTER ABDOMINAL COMPRESS.	AFTER BIAT. JUG. COMPRESS.	AFTER CUFF COMPRESS. OF NECK							
	mm. H ₂ O	mm. H ₂ O	mm. H ₂ O	mm. H ₂ O	cc.	mm. H ₂ O		cu. mm. 9L, 2P, 612 RBC		mg./100	
Oct. 26	380	460	380	10	..	Cloudy	541 WBC (80%L)	++++
Oct. 28	230	Prompt rise	230	..	10	100	Sl. xantho.	3L	++++
Nov. 6	100	120	100	.	10	..	Xantho.	0	++++
Nov. 13	350	350	..	10	130	Xantho.	0	++++
Dec. 1	++++	3570	5555555555
Dec. 13	110	110	110	Xantho.	8L	++++	2590	5555555555
Jan. 11	130	..	130	130	.	.	Xantho.	10L	++++	5555555555, 5555432000
Feb. 11	165	275	165	165	15	0	Sl. xantho.	0	++++	438	5555555555, 4311000000
Mar. 11	170	300	170	170	20	0	Sl. xantho.	8L	++++	237	55555555433
Apr. 22	215	300	215	215	20	75	Colorless	1L	++++	153	5555555543
May 31	185	250	185	185	15	120	Colorless	5L	+++	114	5555554431

back to camp on October 24, he vomited twice and was extremely drowsy. He fell asleep, and there followed a period of amnesia lasting for 5 days. He was taken to the Marine Hospital in Pittsburgh and transferred to the Station Hospital at Indiantown Gap on the same day.

Physical examination at that time showed a temperature of 101°F., a pulse of 70 and respirations of 20. The patient was disoriented and confused, and complained of headache and stiffness of the neck. The pupils were equal, reacted to light and were in accommodation. Extraocular movements appeared normal, as were the eyegrounds. There was marked nuchal rigidity. The other positive findings included lower abdominal tenderness, an enlarged and tender right inguinal lymph node, a urethral discharge and positive Kernig and Brudzinski signs. All the reflexes were active and equal, and there were no motor or sensory changes.

The red-cell count was 4,850,000, and the hemoglobin 90 per cent. The white-cell count was 18,400, with 72 per cent neutrophils, 26 per cent lymphocytes and 2 per cent monocytes. The urine was normal. Smears of the urethral discharge revealed many pus cells but no gram-negative intracellular diplococci. A blood Kahn test made on October 29 was doubtful but negative on the following day. A blood culture was negative after 7 days.

Spinal-fluid examination on October 26 revealed the initial pressure to be equivalent to 380 mm. of water (Table 1). Abdominal compression caused a prompt rise in pressure, but there was no increase with jugular compression. The fluid was slightly cloudy, with 612 red cells and 11 white cells per cubic millimeter. The globulin reaction was +++++. Smears of the fluid, as well as those of all subsequent fluids, were negative for organisms, and cultures showed no growth. Roentgenologic examination of the chest and skull failed to reveal any significant pathologic change.

The temperature gradually returned to normal over a period of 7 days, the pulse rate increasing as the temperature declined. The patient's confusion became much less and he appeared less toxic. The signs of meningeal irritation, however, persisted as severely as before. A second lumbar puncture on October 28 showed that the pressure was elevated and again gave signs of block. The fluid was xanthochromic.

thighs off the bed, but had a fair grip in the hands and fairly strong movement of the toes and feet. The musculature of the extremities was flabby, but fibrillations were not present. The deep tendon reflexes were uniformly hypoactive, whereas abdominal reflexes were absent. To all forms of sensation there was a glove-and-stocking type of hypesthesia, extending to the level of the wrists and to the junction of the middle and lower thirds of the legs.

A lumbar puncture on December 13 showed no change in the fluid dynamics. Neck compression by means of a cuff at 40 mm. of mercury elicited no response. The fluid contained 8 lymphocytes per cubic millimeter and a total protein of 2590 mg. per 100 cc., and the colloidal-gold curve was 5555555555. Wassermann tests, as well as Kline diagnostic and inclusion tests and Kolmer complement-fixation tests, on this and all subsequent spinal fluids were negative.

Slow but steady improvement followed, although therapy was nonspecific. Late in December, lymphogranuloma venereum was first suspected as the causative agent. A Frei test was done, using antigen of chick-embryo origin, but was negative. This was repeated on January 10, 1943, and was again negative. The spinal fluid was examined on the following day, with essentially no change from the preceding findings. At that time the colloidal-gold curve in a 20-tube test was 5555555555, 5555432000. Mice were inoculated intracerebrally and intraperitoneally with portions of this spinal fluid, but no virus was isolated. Complement-fixation tests on serum obtained on January 15 were strongly positive for the lymphogranuloma-psittacosis group (Table 2). Further Frei tests were carried out, using both chick-embryo and human antigens, the former yielding a questionably positive result, whereas the latter was negative (Table 3).

By that time the patient had improved sufficiently to be able to walk around, but still complained almost daily of bi-frontal and occipital headache. There was also pain in the cervical region and upper dorsal spine. This pain was made worse by sudden acute flexion or extension of the head.

On February 22, the single enlarged right inguinal lymph node was surgically removed and half of it sent to the Virus Laboratory of the Army Medical School. From it a virus was isolated and identified as that of lymphogranuloma

venereum. Therefore, beginning on March 3 and continuing through March 26, the patient was given 5 gm of sulfathiazole daily. A few days prior to the institution of this therapy the urethral discharge had spontaneously ceased. A further attempt was made to isolate virus from the spinal

TABLE 2 Serum Dilutions Resulting in Positive Complement Fixation Tests with Various Antigens

SOURCE OF SERUM	TIME AFTER ONSET	L A ANTIGEN	LYGRANUM C F	PSITTACOS ANTIGEN
Case 1	mo			
November 9 1941	13½	1:128	1:64	1:256
January 15 1943	3½	1:256	1:64	1:512
April 16	6½	1:128	1:32	1:256
May 24	7½	1:64	1:16	<1:6
May 28	7¾		1:16	<1:12
June 4	8	1:96	<1:8	
Case 2	1	1:32	1:64	1:144
Known case of psittacosis		1:16	1:32	1:32
Normal subject		0	0	0

fluid drawn on March 11, but it was unsuccessful. It should however be noted that the sulfathiazole level of this specimen was 0.85 mg per 100 cc.

By April 9 the patient was feeling much stronger with only mild weakness of the extremities and the sensory deficit had disappeared. Headache was still present but was not so

Fifteen urine examinations were essentially negative. Urethral smears were repeatedly examined for gram negative intracellular diplococci, but all were negative. Three urethral cultures for gonococci were negative.

Routine x-ray examinations of the skull, chest and cervical spine were negative as were special roentgenologic studies of the cervical and dorsal spine and the skull.

December 24 showed sinus 8 per second. The pulse rate was 95 per second on March 8 and about 10 per second on March 30. In each test there was a marked build up with overventilation, with a slow return to the resting state.

The final clinical diagnosis was myelomeningoencephalitis with adhesive arachnoiditis secondary to lymphogranuloma venereum.

CASE 2. L. B., a 22 year old Negro private was admitted to the Station Hospital at Fort Bragg, North Carolina, on July 30 1941. He gave a history of having had coitus without prophylaxis on July 7. Swelling and tenderness appeared in the right inguinal region on July 15 and progressed to the time of admission.

Physical examination was negative except for the painful and tender right inguinal adenitis. The urine was normal.

On August 7, the red cell count was 4,930,000 and the white cell count 14,600. A lumbar puncture on August 7 revealed the spinal fluid to be under slightly increased pressure. There were 483 white cells per cubic millimeter, with 75 per cent lymphocytes and 25 per cent polymorphonuclear

TABLE 3 Frei Tests in Case 1 with Various Antigens

DATE OF TEST	TIME AFTER ONSET	HUMAN ANTIGEN	LYGRANUM S T	A M S ANTIGEN	L A ANTIGEN	PSITTACOS ANTIGEN
December 26	mo					
January 10	3		—			
January 30	3½		—			
February 5	4			±		
May 25	4¾	—				
June 1	7¾		+		+	
	8			+		—

at this hospital was continued so that by June the patient was discharged home on sick leave. At that time the spinal block was still present. In addition Frei tests with Lygranum S T and other yolk sac antigens were positive.

Studies were made with a complement fixation summarized as follows:

Other findings were as follows: Sixteen c. made with a normal ran. The initial white cell count was 160 with 72 per cent neutrophils and 26 per cent lymphocytes. Subsequent counts ranged from 5800 to 11,500, with an essentially normal differential except for a mild degree of eosinophilia (3 to 9 per cent). On February 21, 1943 the clotting time was 4 minutes and the bleeding time 2 minutes. The sedimentation rates in three determinations made over a 4-month period were 20, 20 and 17 mm per hour. A blood culture taken during the acute febrile phase of the illness showed no growth after 7 days. A doubtful Kahn test was obtained from the serum of October 28, but all subsequent tests were negative. Complement fixation for meningococcal, cytotoxic meningitis, Lateral equine encephalitis negative.

An intradermal tuberculin test made on May 27, 1943 with 0.00002 mg PPD (purified protein derivative) was negative, but one made with 0.005 mg PPD on June 4 was positive.

Blood chemistry studies made on December 15 1942 showed the sugar level to be 114 mg per 100 cc and the urea level 9 mg. On December 8, the total protein determination was 7.84 gm per 100 cc with 4.57 gm of albumin and 3.27 gm of globulin per 100 cc. On April 8 1943, the total protein was 9.0 gm, with 4.82 gm of albumin and 4.18 gm of globulin.

leukocytes. Smears showed no organisms and cultures were negative. On August 11 a Frei test was positive.

On August 4 the patient developed frontal and occipital headache and photophobia. This persisted for the next 3 days and then subsided. The temperature during that time was between 100 and 101°F.

A clinical diagnosis of meningoencephalitis secondary to lymphogranuloma venereum was made.

Serum taken from the patient on August 16 and stored at -20°C was tested 21 months later and gave a positive complement fixation reaction for lymphogranuloma venereum in dilutions up to 1:64 (Table 2).

VIRUS STUDIES

Although in Case 1 an association between the findings in the central nervous system and lymphogranuloma venereum was suggested by the positive complement-fixation tests, it was thought that isolation of the virus would offer more conclusive evidence of such a relation. Accordingly, efforts were made to isolate virus, even though a considerable interval had elapsed after the acute febrile phase of the illness. These studies are described below.

Cerebrospinal fluid. Bacteriologically sterile specimens of spinal fluid were obtained on January 11 and March 11, 1943, for attempts at isolation of virus. Mice were inoculated intracerebrally and intraperitoneally with 0.03 cc. and 0.1 cc of the fluid, respectively. None of these animals showed clinical evidence of disease. Several passages were

made in an effort to bring out possible unapparent infection, but without success. All the mice not sacrificed for passage were tested intracerebrally for immunity to lymphogranuloma venereum virus, and were found to be nonimmune.

Lymph node. The right inguinal lymph node noted in the clinical record was removed on February 22, about five months after it had appeared. Grossly, it measured 15 by 10 by 7 mm. and was grayish-white, with a slightly nodular surface. It was sectioned with ease, revealing a 3-mm. rim of lymphoid tissue supported on fatty tissue. Half the node was reserved for virus study and the remainder was fixed for pathological study. Sections of this material were studied at the Army Medical Museum, where the following description was made:

The lymph node is the seat of low-grade chronic inflammation of nonspecific character as judged by the histopathologic appearances. The capsule is thickened and infiltrated by lymphocytes and plasmocytes, and the trabecular and hilar connective tissue is increased in amount. The follicles are hypertrophied and there is considerable mitotic activity in the germinal centers. The lymphoid and reticuloendothelial elements of the node are hyperplastic, and the latter are actively phagocytic, containing nuclear debris and occasional brown pigment resembling melanin. There is no suggestion of the tubercloid lesions of lymphopathia venereum. Diagnosis: chronic hyperplastic lymphadenitis, nonspecific.

At the Virus Laboratory, smears were made from the cut surface of the lymph node and stained by the Macchiavello technic. Several minute red bodies resembling the elementary bodies of lymphogranuloma venereum were observed. Blood agar cultures of this material were negative. A portion of the node was ground, suspended in saline solution and injected intracerebrally and intraperitoneally (0.03 cc. and 0.2 cc. of a 10 per cent suspension, respectively) into 6 mice. One mouse appeared ill on the fourth day and was sacrificed. A 10 per cent suspension of the brain was injected intracerebrally into other mice. Cultures of the inoculum were negative. Three more of the original 6 mice showed signs of illness from which they slowly recovered, but the 2 remaining mice failed to become ill.

All the second-passages mice showed evidence of disease four to six days following inoculation. Macchiavello-stained touch smears of the meninges revealed elementary bodies of the lymphogranuloma venereum type, whereas bacteriologic cultures were negative. The virus* was maintained by intracerebral passage in mice.

Characteristics of the Virus

Mice. The L. A. virus was carried through thirteen successive mouse passages before being stored at -70°C . In these animals, following intracerebral inoculation the disease was characterized by roughening of the fur, hunching and weight loss. Frequently, the first sign of illness was that of

hyperactivity induced by tactile stimuli, often ending in a tetanic convulsive seizure, with or without death ensuing at that time. Not infrequently, mice passed through this phase of hyper-reactivity into a longer period of apathy, with hunched backs, roughened coats and emaciation. In two or three weeks gradual improvement followed, with apparent clinical recovery. Such mice were usually immune to subsequent reinoculation with the virus.

Brain material from the fourth mouse passage was titrated intracerebrally in mice. Half the mice died in each tenfold dilution through 1:10,000. The remaining mice became sick through dilutions of 1:1,000,000 and then slowly recovered.

Intraperitoneal inoculation with 0.1 to 0.2 cc. of a 10 per cent suspension of fresh infected mouse-brain material did not give rise to clinical disease. Three or four such injections at intervals of a few days to a week usually resulted in immunity to intracerebral inoculation with the homologous strain.

Guinea pigs. Two adult male guinea pigs were inoculated with a 10 per cent suspension of infectious brain material from the third mouse passage, each receiving 0.1 cc. intradermally and 1.0 cc. subcutaneously in the inguinal region. Both animals developed moderate fever — one from the second to the fourth day, the other on the fifth and sixth days. Inguinal adenopathy appeared in one animal, which also developed a vesiculopustular lesion at the site of intracutaneous injection. A red papular lesion was produced in the other animal. Both skin lesions gradually subsided in a few days.

Developing chick embryos. A bacteriologically sterile 10 per cent suspension of infectious brain material from the second mouse passage was inoculated in 0.2-cc. amounts onto the chorioallantois of ten-day developing chick embryos. By the fifth day, central plaque lesions and numerous secondary pocklike foci appeared in about half the eggs. These lesions were usually whitish and opaque, but occasionally clear vesicles were produced. Smears stained by Macchiavello's method showed occasional elementary bodies and plaques. One of the infected membranes was ground into a 10 per cent suspension, and other embryonated eggs were inoculated. Ten-day embryos received 0.2 cc. on the chorioallantois, whereas six-day embryos had 0.5 cc. injected into the yolk sac. About half those inoculated on the chorioallantoic membrane developed lesions. This type of passage was then discontinued.

Of 6 embryos inoculated in the yolk sac, only 1 was heavily infected when examined ten days after injection. This yolk sac was ground, a 1:10 suspension was made, and 0.5 cc. was inoculated into the yolk sac of additional six-day embryos. The L. A. virus was carried through thirteen successive yolk-sac passages before being stored at -70°C . During this series of passages, the best yield of elementary bodies resulted when seven-day or eight-day embryos were inoculated with 0.5 cc. of a 1:50 dilution

*The virus isolated from Case 1 is referred to throughout as the "L. A. virus."

of infected yolk-sac material. Such embryos usually died four to six days after inoculation.

Studies to Establish the Identity of the Virus

The manifestations of infection with L. A. virus in the mice, guinea pigs and developing chick embryos were consistent with those described by others^{2,7,9-11} for lymphogranuloma venereum. In addition, parallel infection experiments with a known strain of lymphogranuloma venereum virus were carried out in mice (five passages) and chick embryos (thirteen yolk-sac passages), with essentially identical findings.

The pathologic changes induced in mice intracerebrally inoculated with the L. A. virus were also comparable with those known to occur in these animals when infected with lymphogranuloma venereum.⁷ Polymorphonuclear and round-cell infiltration of the meninges was the most striking feature. Although perivascular cuffing of moderate degree was observed, the involvement of the brain substance was minimal.

Further information concerning the identity of the L. A. virus was obtained from cross-immunity tests in mice. The animals were immunized to the virus by repeated intraperitoneal injections* of infectious mouse-brain suspensions. Inoculations were made at intervals of a few days to a week or more, a total of four or five injections of 0.1-cc. amounts being made before a final intracerebral inoculation was made with the homologous virus. Similarly, mice were immunized to a known strain of lymphogranuloma venereum virus. The injected mice were then tested intracerebrally with 0.03 of a fresh 10 or 20 per cent suspension of infectious mouse-brain material of the

antigen made from the virus isolated from the patient and hence labeled "L. A. antigen." Lygranum C. F. is a commercial preparation (Squibb) from yolk-sac material infected with lymphogranuloma venereum virus. It has been used extensively in complement-fixation tests for this disease.^{6, 13, 14} The other two antigens were also prepared from infected yolk-sac material using an ether-extraction method. This technic has been applied to the lymphogranuloma-psittacosis group of viruses by several workers.¹⁵⁻¹⁷ Only those yolk sacs that appeared rich in elementary bodies were used in the preparation of the L. A. antigen. Before inactivation of the material, it was titrated intracerebrally in mice. It was found to make all the mice definitely ill in ten-fold dilutions through 1:100,000; however, deaths were few and were distributed unevenly in the various dilutions.

FREI TESTS

The above laboratory data indicated that the patient had had active lymphogranuloma venereum infection for at least six months. During that period, however, four Frei tests had been made, with only one questionably positive result (Table 3). A new series of Frei tests was therefore carried out, using antigens of chick-embryo origin.^{12, 18} These antigens included the commercial product (Lygranum S. T.); the Frei antigen of the Army Medical School and the L. A. antigen, made from the patient's virus. In addition, it was of some interest to use properly diluted psittacosis antigen in skin tests on the patient, since serologic studies had brought out the usual cross reaction noted for this group of viruses.¹⁹ The last two antigens were diluted in the following manner: yolk sacs were calculated to weigh 1.5 gm. each, and the dilutions were made up to 1:25, 1:50 and 1:75 — that is, 1 part of infected yolk sac was suspended in 25 parts of buffered-saline solution and so forth. Similar dilutions of normal yolk-sac suspensions were used as controls. For testing, the usual 0.1-cc. intradermal injection of each dilution was made, and daily measurements of the lesions were made for seven days. As can be seen in Table 3, Lygranum S. T., the L. A. antigen and the Army Medical School antigen gave positive results, whereas the psittacosis antigen was negative.

DISCUSSION

The diagnosis of these cases as lymphogranuloma venereum was based on the clinical history and physical findings, the positive complement-fixation tests, the positive Frei tests and, in Case 1, the isolation of the virus from the patient. The etiologic relation of the virus to the meningoencephalitic changes is, of course, based on circumstantial evidence — that is, the involvement of the central nervous system along with the virus infection, the knowledge that this virus can produce meningoencephalitic signs in experimental animals, the fact that the virus has been isolated from *

TABLE 4. Cross-Immunity Tests in Mice.

EXPERIMENT No.	IMMUNIZING VIRUS	TESTING VIRUS	RESULTS OF TESTS*	
			IMMUNIZED MICE	NORMAL MICE
1	L. A.	A. M. S.	0,0,0,0,0,0,8†	3,7,8,11,5,5
	A. M. S.	L. A.	0,0,0,0,0,0,0	2,2,4,4,4,5
	A. M. S.	L. A.	0,0,0,0,0,0	3,4,5,5,5

*The numeral indicates the day of death of the mouse following the test inoculation. S, indicates that the animal showed definite signs of illness but survived at least ten days, 0 means that the animal remained well throughout.

†This mouse probably died of intercurrent infection

heterologous strain. Control mice were inoculated in each case. The animals were observed daily. The findings, which are presented in Table 4, strongly indicate similarity of identity of the L. A. and the known lymphogranuloma venereum strains of virus.

Complement-fixation studies were utilized not only to determine the presence of specific complement-fixing antibodies in the patient's serum, but also as an ancillary aid in identifying the virus isolated from him. The findings are summarized in Table 2, from which it can be seen that these tests were carried out with three different antigens, namely, Lygranum C. F., psittacosis antigen and an

Sabin and Aring reported inability to immunize mice by intraperitoneal inoculation with strains of virus isolated from their patient, as well as with known lymphogranuloma venereum virus

other patients with the disease^{3, 6} and the negative serologic results in tests against other encephalitis-producing virus agents. Final proof that lymphogranuloma venereum can cause meningoencephalitis in man must await isolation of the virus from the brain substance in a fatal case and the demonstration of histopathologic changes in the brain tissue consistent with those produced by the virus in experimental animals.

On the basis of the spinal-fluid dynamics (Table 1), Case 1 presented a complete spinal block throughout the eight months he was observed. It is believed that the meningeal involvement early in the course of his illness resulted in subarachnoid block. This syndrome is known to occur in patients with acute purulent meningitis, tuberculous meningitis, yeast meningitis and syphilitic meningitis.²⁰ Since these causes seem to have been excluded by means of cultural and serologic studies, it appears probable that the adhesive arachnoiditis encountered in this case was a residuum of the lymphogranuloma venereum infection.

In addition, certain other features of the spinal-fluid findings are of interest. The total protein content reached 3570 mg. per 100 cc., gradually diminishing in amount as the patient improved. None of the specimens clotted after standing. The question arises whether the great increase in protein content was the result of the subarachnoid block per se, of the meningeal involvement or of both these factors. Such high levels of protein are encountered extremely rarely, even in the presence of cord tumor.²⁰ In this patient, the amount of protein gradually declined from 3570 to 114 mg. per 100 cc. It does not appear that this decline was due to the progressive removal of protein by repeated lumbar punctures, since the intervals between them were about the same both when the protein content was extremely high and when it was relatively low. This suggests that the accumulation of protein occurred at a progressively diminishing rate and was therefore not caused by the block alone. Furthermore, Sabin and Aring⁶ found that the amount of protein reached 1400 mg. per 100 cc. in the spinal fluid of a patient who presented no evidence of obstruction. Thus, although in the present case the subarachnoid block undoubtedly was a factor, the more important cause of the great increase of spinal-fluid protein was probably the meningitis, which in turn was probably due to lymphogranuloma venereum.

It is of additional interest to note the character of the colloidal-gold curves, which were uniformly of the paretic or first-zone type. On two occasions, twenty-tube tests were performed in order to obtain end-point readings, and the curves were 5555555555, 5555432000 and 5555555555,4311000000, respectively. Merritt and Fremont-Smith²⁰ have concluded on the basis of their wide experience that this test has no specific diagnostic import and that precipitation of the colloidal-gold solution is indicative only

of an abnormality in the protein content of the fluid. That this was the case in this patient appears to be borne out by the data presented in Table 1.

Infection with the lymphogranuloma venereum virus is known to persist for a long time,² so that it is not surprising that the L. A. virus was isolated from a lymph node that had been slightly enlarged for five months. It seems significant, however, that the histopathologic changes observed in this node were nonspecific and not at all suggestive of involvement with this virus.

Isolation and identification of the virus is a too elaborate and slow procedure to be used for routine diagnostic purposes. The complement-fixation test thus becomes an especially valuable adjunct in the early diagnosis of infection with the lymphogranuloma-psittacosis group. Unfortunately, with the antigens now in use it is not possible to differentiate these closely related viruses.¹⁹ This similarity was observed in the complement-fixation results with the serums from these two cases (Table 2) and, as mentioned before, other evidence is necessary in order to establish the diagnosis.

The complement-fixation test was also used as a means of identifying the L. A. virus. An antigen was made from yolk sacs infected with the L. A. virus and was used in tests with serum from both patients and from a known case of psittacosis. Positive reactions were obtained with all the serums.

Negative results with Frei tests are not infrequently observed in lymphogranuloma venereum infections. Only one of eight tests done in the case reported by Sabin and Aring⁶ was positive. In Case 1, positive tests were not obtained until the eighth month of illness, and included a positive reaction to an antigen prepared from the virus isolated from the patient. Because of the cross reactions noted in the complement-fixation studies, he was also tested against a psittacosis antigen, with a negative result. So far as could be ascertained, there have been recorded no extensive series of tests on known lymphogranuloma patients with psittacosis antigen, so that the significance of this single observation cannot be evaluated.

SUMMARY

Two cases of meningoencephalitis in patients with lymphogranuloma venereum are presented.

A virus was isolated from an inguinal lymph node of one patient five months after the onset of illness, in spite of the fact that the histopathologic changes in the lymph node were nonspecific.

The virus was identified as lymphogranuloma venereum by its effect in mice, guinea pigs and developing chick embryos, by cross-immunity tests in mice and by complement-fixation studies.

Mice were immunized to this virus and to another strain of lymphogranuloma venereum by intraperitoneal injection.

Subarachnoid block, an extremely high total protein and first-zone colloidal-gold curves were observed in one patient. These findings are discussed.

Positive Frei tests were obtained on one patient with an antigen made from the virus isolated from him, as well as with other yolk-sac antigens. An intradermal test on the same patient with psittacosis antigen was negative.

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CARCINOMA OF THE THYROID GLAND WITH A SOLITARY METASTASIS TO THE SKULL

Report of a Case

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THE characteristically slow growth of the solitary metastasis of carcinoma of the thyroid gland to bones, notably to the skull, has been repeatedly observed. In 1871, Mueller¹ noted the tendency of metastatic lesions of the thyroid gland to appear microscopically benign. Cohnheim² was led to regard the primary thyroid lesion as a so-called "benign metastasizing adenoma." He used this paradoxical term in an attempt to explain the long-standing presence of the primary tumor in the thyroid gland and of metastasis to the skull without the usual progressive spread and early death so often seen in other forms of malignancy. More recent studies by Simpson,³ Dinsmore and Hicken⁴ and Graham,^{5, 6} and the opinions cited by Turner and German⁷ after their recent careful review of the literature have led to the conclusion that there is no such entity as a benign metastasizing adenoma. Turner and German believe that this type of thyroid tumor is actually a malignant adenoma. In their experience, painstaking microscopic examination of the entire tumor has, in most cases, shown tumor-cell invasion of the blood vessels, stroma or capsule of the adenoma.

These slowly growing metastatic lesions in the bones, prominent in the skull, vertebrae and pelvis,

may be solitary or multiple. In some cases the lesion may exhibit arterial pulsation, but this is not always present. Because of the slow growth and the relatively isolated nature of the skeletal metastatic lesion, attempts have been made from time to time to remove both the original tumor and the metastatic lesion surgically. In 1941, Turner and German⁷ reported 2 cases in which removal of multiple thyrogenic skull metastases was attempted. The first patient had extensive metastases to the skull but survived the operative removal for three years, ultimately succumbing to progressive metastatic spread. One year after operation, a tender, nodular liver developed, followed by the appearance of further metastases in the skull and in the cervical lymph nodes. The second patient had metastases to the skull, pelvis, coccyx and kidneys at the time of operation and died of uncontrollable hemorrhage following attempted removal of the extensive skull lesions. The hemorrhage occurred during elevation of the bone flap.

Friedman⁸ has recently reported 2 cases operated on subsequent to January, 1942, with immediate success in removal of both the primary thyroid tumor and the skull lesion.

In the case reported herein, there was a visible solitary metastasis to the right temporofrontal region of the skull and a previously unnoticed large

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calcified adenoma of the right lobe of the thyroid gland. Both these findings were regarded as favorable and fortified the opinion of members of the Thyroid Service and the Neurosurgical Service in their deliberations on ward rounds. Thorough discussion led to the ultimate decision to attempt

gland could be felt the upper portion of an extremely hard mass suggesting a calcified adenoma, almost completely sub-sternal. The left lobe was normal. Laryngeal examination showed normal motion of both vocal cords. The remainder of the examination and laboratory studies showed no ab-



FIGURE 1. *Preoperative X-ray Film of the Skull, Showing the Solitary Metastasis in the Right Frontal Area.*

removal, first, of the primary malignant adenoma of the thyroid and then of the skull lesion, which had been proved by biopsy to be thyrogenic.

CASE REPORT

R. S. C., a 52-year-old, Italian housewife, was first seen in the Tumor Clinic of the Massachusetts Memorial Hospitals on December 6, 1940, at which time she complained of a painless lump on the right upper forehead. Four months previously, the lump had appeared immediately after she struck this part of her head against the corner of a medicine cabinet. It had not changed in size and was not painful or tender. She had, however, noted occasional mild right-sided headaches since the injury, and recently a slight discomfort in the region of the lump itself. She stated that her general health was excellent, and that she had no other complaints.

Examination disclosed a mass in the right lobe of the thyroid gland, which the patient had not known to be present. Consequently, she was admitted to the Surgical Service on December 12, 1940, for study. In the right frontal area there was a moderately firm, nontender mass measuring 2.5 by 1.0 cm. This was thought to lie in a bony defect with some elevation of the outer table of the skull. A nonexpansile arterial pulsation was felt, and there was some increase in tension when the patient coughed. In the right lobe of the thyroid



FIGURE 2. *Photomicrograph of a Section of the Thyroid Tumor.*

normalities. A blood Hinton test was negative. Lumbar puncture showed an initial pressure equivalent to 180 mm of water. The spinal-fluid cell count was 3 lymphocytes per millimeter, with the sugar 79 mg. per 100 cc. and the globulin not increased. The gold-sol curve and Wassermann reaction were negative, and the total protein was 16 mg. per 100 cc. The basal metabolic rate was +11 per cent.

X-ray examination of the skull showed a 3-cm. defect in the right frontal area, involving both tables, with slight surrounding condensation of the bone (Fig. 1). X-ray films of the trachea showed some displacement to the left, with lateral and anterior compression. A calcified mass could be

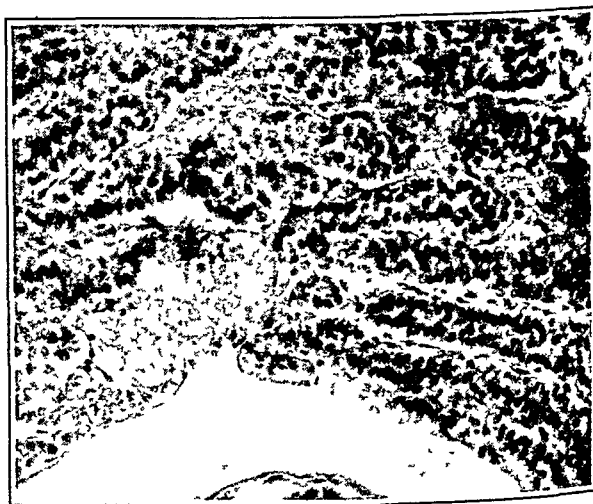


FIGURE 3. *Photomicrograph of a Section of the Skull Tumor.*

seen in the region of the right lobe of the thyroid gland. The chest showed increased fibrosis and no metastases. X-ray films of all the long bones revealed no other lesion. Intravenous pyelograms were negative.

The patient was seen by the neurological consultant, Dr. Theodore J. von Storch, whose impression was that there was no intracranial involvement from the mass other than a questionable slight pressure on the right frontal lobe.

On December 28, Dr Howard M. Clute performed a right total thyroidectomy and a biopsy of the tumor in the right frontal area. Pathological examination of the tissue was reported by Dr Charles T. Branch as follows:

The specimen consists of a lobe of thyroid tissue measuring 8.0 by 4.5 by 3.0 cm and weighing 50 gm., somewhat pear-shaped, the smaller end representing the upper pole. The lower three quarters of the gland is represented by a firm, partially calcified, encapsulated irregularly

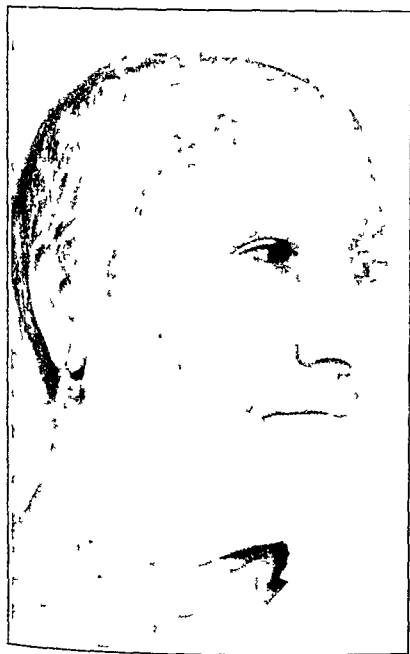


FIGURE 4 Appearance of the Patient Two Months after Removal of the Skull Metastasis

Note the diamond-shaped skull defect, as well as the thyroid scar, three months after removal of the primary tumor

rounded nodule approximately 4 cm in diameter. On section fully two thirds of the central part of this mass is found to be stony hard and calcified. Its periphery, however, is composed of soft, pliable, smooth glistening reddish brown meaty appearing tissue in which no normal acinar tissue can be discovered.

Microscopic section through the nodule shows it to consist of closely set cords of small, hyperchromatic epithelial cells having all the appearance of embryonal thyroid tissue (Fig 2). In certain areas these cords open up to form well defined lumens of fetal character containing a small amount of poorly staining colloid substance. There is definite vascular invasion. In spite of their embryonal nature, careful search shows relatively little anaplasia of the epithelial cells, and mitoses are extremely rare.

Section through the biopsy specimen from the skull (Fig 3) shows a histologic picture practically identical with that above described. Here the cells are slightly more anaplastic, and show a few more mitoses and less evidence of regular alveolar arrangement. Here, also, there is distinct evidence of vascular invasion.

Diagnosis. Thyroid gland small cell carcinoma arising from embryonal adenoma and showing vascular invasion. Skull lesion metastatic carcinoma from thyroid gland, showing local vascular invasion.

The postoperative course was satisfactory, although marked by a rise in temperature to 103° F on the 2nd day, followed by a gradual fall to normal. Both the thyroidectomy and skull biopsy wounds healed well. Much discussion among the surgical staff and the neurosurgical consultant, Dr Donald Munro, led to the belief that in view of the slowly progressive nature of the apparently solitary metastatic tumor, an attempt at radical cure by excision of the skull lesion with subsequent radiation therapy was indicated.

The patient was therefore transferred to the Neurosurgical Service of the Boston City Hospital on January 9, 1941 for further treatment. On January 27 craniotomy was performed by Dr Munro and the metastatic tumor was removed. It was found that although the dura was depressed by the growth, only its outer layer was involved and there was no perforation. Convalescence was satisfactory, and the patient was discharged home on the 10th postoperative day. On this day x-ray therapy was begun consisting of a series of ten doses of 200 r each directed at the right temporofrontal area and given over the course of 1 month.

When seen 2 months after the second operation, the patient had no significant complaints. There was a diamond shaped skull defect measuring 5 by 3 cm (Fig 4), with definite pulsation in the area, but with no palpable masses. The body weight had remained static.



FIGURE 5 Appearance of the Patient Two Years After Operation

When last seen 2 years and 6 months after the second operation the patient was having no difficulty of any sort. She felt entirely well and had gained 6 pounds. There were no palpable masses or evidences of recurrence at either operative site. The defect in the skull had a firm fibrous base giving sound protection to the underlying brain tissue. The patient's appearance was entirely normal with normal coverage and distribution of hair (Fig 5). A check up x-ray examination of the skull in December, 1942 showed a smooth outline of the skull defect with no evidence of recurrence or metastatic spread (Fig 6).

DISCUSSION

The subject of treatment of this disease is a controversial one. In this case, two years of normal health and apparent freedom from metastatic malignant disease seem to have validated the judgment of the physicians involved. Some writers have expressed reluctance to subject a patient to such

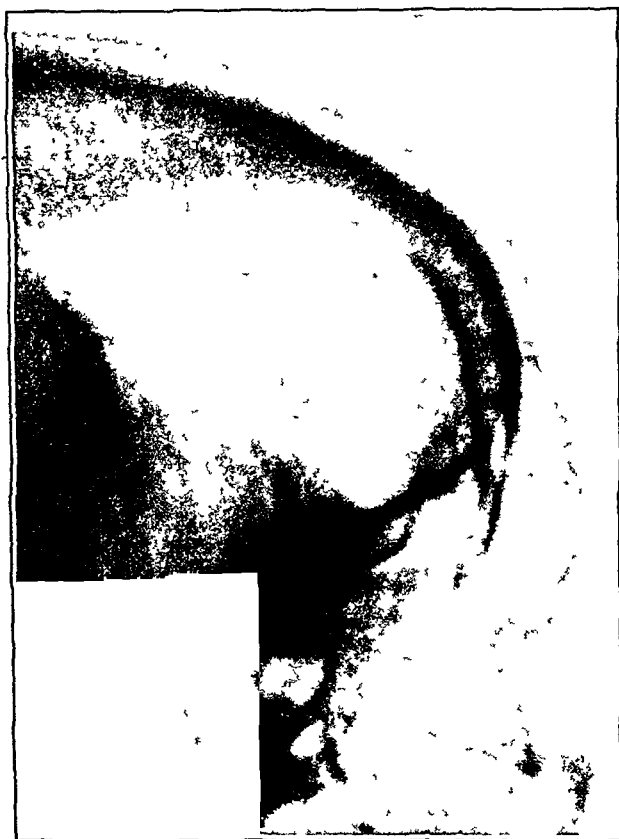


FIGURE 6. X-ray Film of the Skull Two Years after Operation.

Note the smooth bony outline of the defect.

radical palliative surgery. Hamann,⁹ in reporting a nonoperable case in 1916, expressed the then prevalent opinion as follows:

As has been pointed out by Bland Sutton and others, metastatic deposits in the skull, manifesting themselves as pulsating, vascular tumors, occur sometimes, secondary to thyroid carcinoma; such metastatic growths are, of course, quite inoperable, as the writer can confirm from an experience in one case in which attempt to remove the growth had to be desisted from, owing to the large size of the blood-vessels.

Cruickshank,¹⁰ however, in 1938 reported the successful removal of a tumor from the right frontal area of a fifty-five-year-old Hindu woman. This tumor was thought to be a meningioma, but pathological examination revealed typical thyroid tissue. Control of hemorrhage had not been troublesome. Four months later a nodule the size of a hazelnut was discovered in the right lobe of the thyroid gland, but the patient refused further operation,—that is, thyroidectomy,—and follow-up studies were not reported.

Barthels¹¹ has stated that the carcinoma of the thyroid gland that produces bone metastases is of relatively low virulence, and that therefore to remove a single metastatic lesion cannot be described as meddlesome surgery.

Neither the thyroidectomy nor the skull operation proved to be of such formidable nature as to cause severe discomfort or to occasion a prolonged hospital stay. The patient left the hospital seven days after the thyroidectomy and ten days after partial craniectomy, without further disability. Her further course will be studied with interest. Certainly effective palliation has been gained in a situation that had appeared advanced and inoperable.

SUMMARY

The case of a patient who had a carcinoma of the thyroid gland and a single skull metastasis and who showed no evidence of recurrence two and a half years after the surgical removal of both lesions is presented, and pertinent references in the literature are discussed.

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MEDICAL PROGRESS

GYNECOLOGY: CARCINOMA OF THE CERVIX

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CARCINOMA of the cervix is the commonest malignant tumor occurring in the genital tract in women, ranking closely in frequency with cancer of the breast. Its presence may be detected extremely early, for among its symptoms are bleeding and discharge. The tumor can be seen and felt, and is accessible to biopsy. The new vaginal smear technic,¹ which will be described later, also enables its presence to be detected.

The results of treatment, either radiologic or surgical, are excellent in early cases, yet this disease is found in its early stage in not over 20 per cent of patients seen. The present review of the progress made in all phases of cervical cancer shows that although the results should be markedly improved, they are not. Lack of careful periodic examination of the cervix, appreciation of the significance of abnormal discharges and bleeding and of frequent biopsy of the cervix accounts for many advanced cases. It is also true that patients who have had no symptoms are seen with advanced disease. There is ample evidence, however, that more careful attention to early symptoms and more careful investigation by physicians would result in surgical treatment in the early stages. The results of treatment seem to have reached a level beyond which it is difficult to go. There is no doubt that certain specially treated and studied groups of cases do better than those routinely treated, but on the whole most of the results of the largest cancer clinics show about the same percentages of arrested or cured cases. In other words, it is obvious that more cures will come from earlier diagnosed cases and also from more individualistic treatment.

The theory that all cases should receive combined radium and x-ray treatment, in a routine manner, is not sound. The radiologist should see the tumor and map it out so that he can better aim his x-ray tube at each treatment. The radium available should be of all types and strength. The choice of applicators and needles should be made at the time the treatment is given and not planned before the patient is under an anesthetic, or before x-ray treatment is completed if the latter is given before the radium treatment. Most clinics have radium in certain strengths and in certain types of needles, and thus limits the possibility of variation in its use.

The tendency is to have rules for treatment of the various classes of the disease and to give the treatment always in the same manner. Instead, it should be varied to meet the type and extent of the disease in each case. Every clinic has its set method of treatment, and in each the operators are convinced of the perfection of their method, yet, as already stated, in the end the largest clinics have the same percentage of cures. It is therefore obvious that new methods of attack on the problem must be tried and that treatment should be directed to the cure of the patient whether or not it consists in the giving of x-ray or radium or in surgery. Tausig's² work, to be discussed later, is an example of individualization of cases and the results of his method of treatment are, in his hands, strikingly better than those in most clinics. Miller,³ of the University of Michigan Hospital, expresses the following viewpoint, which is probably the correct one.

The limitations of existing methods of treatment are well recognized. No one expects the impossible but there is good reason to believe that therapy is disappointing. We appear to have reached that comfortable state wherein we hesitate to disturb the efficiency of a therapeutic system which has taken a long time to establish. Perhaps well as the apparent effective has lulled us into a state of exploit existing methods of

treatment to their fullest capacity. In radical abdominal hysterectomy, as first performed by W. A. Freund in 1878 and later popularized by Wertheim, was recognized a potent weapon for combating cervix cancer. But because of its high primary operative mortality rate and its restricted field of usefulness the operation was permitted to pass into the discard. Radium and x-ray have also proved their worth. Yet after almost a quarter century devoted to the refinement of technic and stabilization of procedure I find there is little to boast about. Perhaps we have reached the end of an era. Perhaps if we could see into the future we might visualize as the cancer therapist not the radiologist nor the gynecologist nor the surgeon but possibly the chemist. It is not beyond the realm of possibility that radium may some day become a drug on the market and deep x-ray therapy equipment an excellent source of copper wire and other spare parts. The limited capacity of existing remedial measures is definitely responsible for some of our restricted success but any attempt to blame results on this basis alone might more properly be attributed to an indolence on our part—a failure to exploit to their fullest efficiency radium x-ray and surgery or a combination thereof—a serious failure to give these methods of treatment a fair chance. In both irradiation therapy and surgery we have potent weapons. Perhaps neither has been developed to its fullest efficiency. Given an opportunity, these methods may still accomplish what we have a right to expect in the way of vastly improved survival rates.

It is certain that advances will be made in the treatment of this condition. Papinicolaou and

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Traut's⁴ work on the vaginal smear, Schiller's^{5, 6} observations on the staining of the cervix, Hinselmann's⁷ use of the colposcope, Taussig's² demonstration of the ease and efficacy of lymph-node dissection and our own demonstration⁸ of the safety of the radical operation for cervical cancer, when aided by the methods of modern surgery, furnish evidence that more possibilities are open now than ever before.

ETIOLOGY

There is no doubt that most cancers of the cervix occur in women who have borne children, but nulliparas make up 5 to 10 per cent of the patients seen in cancer clinics. It is possible that the important factor is not the lacerations themselves but the resultant infections and irritations. Thus, in nulliparas who develop this disease it is conceivable that an endocervicitis or some such lesion as a so-called "congenital erosion" of the cervix has been present. A young girl with menorrhagia recently seen in our clinic had such an erosion. Ten years later the whole area affected was replaced by carcinoma.

Wharton⁹ quotes Pearl as stating: Of 100 American women about 70 are parous and 30 nonparous. In other words, their ratio is as $2\frac{1}{2}$ to 1, but the incidence of cervical cancer, on this basis, is as 19 to 1. In other words, with due correction cervical carcinoma is approximately eight times more frequent in parous than in nonparous women. These data indicate that pregnancy or labor does something which predisposes toward cervical cancer.

Severe irritations of the cervix, such as those occurring in patients with procidentia, rarely end in cancer.

Sorba¹⁰ believes that syphilis plays a part in the development of cervical cancer, for 262 patients, or 14 to 15 per cent, of those seen in his clinic had the disease, whereas the percentage of syphilis in other patients was only 1.6 per cent. He thinks that syphilis gives impetus to the cancer. Reports from American clinics do not give such high percentages of syphilis in patients with cancer of the cervix.

Heredity probably plays a role in the etiology of tumors, but a family history of carcinoma is not often present. Imamura¹¹ found such a history in 9.4 per cent of patients with tumors of the uterus. Wassink,¹² of Holland, in discussing carcinoma of the breast, stated that in many cases there was a family history of carcinoma of the uterus. In our clinics at the present time there are two pairs of sisters with cervical cancer. There is probably a certain amount of truth in the theory of heredity, but in the large majority of cases no family history of cancer is found.

It is interesting to note the infrequency of cervical cancer in Jewish women. Smith¹³ found it to be about 5 per cent in the clinic of the Memorial Hospital (New York City), and Healy and Twombly,¹⁴ reporting from the same clinic, stated that only 5 per cent of 920 women patients were Jewesses. This absence of cervical cancer in Jewish women can

be explained by breeding out of the disease, since it is apparent that Jews have bred in diabetes and hypertension, or by the Mosaic law in relation to sex, for observance of this law results in the fact that intercourse does not occur during or shortly after the period, when the cervix has just gone through the changes incident to menstruation.

Theories of a hormonal origin have been proposed, and both the pituitary gland and the ovary are considered as possible etiologic factors. Hofbauer¹⁵ believes that the influence of the pituitary gland on the cervix is great, yet this influence must not be direct but through the ovary, which produces estrin and progestin under pituitary influence. Estrin is a growth-producer and is responsible for changes occurring in the cervix. It is well known that Hisaw¹⁶ has been able to produce cancerlike lesions in the cervix with estrin, but the lesions are not real cancers, and are cured by progestin. It is also known that cervical polyps may take on a cellular activity that is similar to cervical cancer during pregnancy. The polyps have a cancerlike appearance when examined microscopically but are not true cancers. The changes are due to some hormonal influence, probably that of estrin. Gardner, Allen, Smith and Strong¹⁷ have been able to produce cancer in the cervixes of mice by the use of estrin. These tumors metastasize and can be grafted and grown without more estrin. Other experimenters have produced cancer with estrin in other organs in the animals, but there is no proved case of production of the disease in a human being in this manner. In patients with cancer of the genital tract, however, estrin therapy should be avoided until it has been proved to be safe.

There is no known etiologic factor in cervical cancer, but childbearing, lacerations, infections, syphilis, hormones and heredity all play a part. A tendency to cancer must be present, and some other factor must be the spark that starts the fire.

SYMPTOMATOLOGY

No new symptoms have been described to suggest the presence of cancer of the cervix, but meticulous attention must be paid to abnormal bleeding or discharge, whether spontaneous or following douching or intercourse. When continuous bleeding, discharge or pain occurs, the cancer has probably grown beyond the early stage. Miller¹⁸ states that the most significant early symptom is abnormal bleeding.

DIAGNOSIS

There have been added to current diagnostic methods three extremely valuable aids.

Schiller's⁶ test is valuable if its indications are interpreted correctly. Schiller used Lahm's discovery that in cancer of the cervix the epithelium lacks glycogen, which is present in normal cervical epithelium. He therefore thought of iodine, which

stains glycogen, as a test for its absence. He advocates a solution made up of 1 part iodine, 2 parts potassium iodide and 300 parts distilled water. In our clinics this solution has not been found satisfactory, since it stains too lightly; the amount of iodine has therefore been increased to 2 parts and that of potassium iodide to 4 parts. This solution is highly satisfactory. Iodine is poured into the vagina, left for two or three minutes and gently reabsorbed with cotton, and the cervix is then viewed.

The most valuable aid that can be obtained from Schiller's solution is indication of the area from which a biopsy specimen should be taken. Any area that stains a homogeneous dark brown can be considered normal, and any area without a stain should be biopsied. Light-brown areas are usually those of diseased or infected epithelium. Superficial cancer does not stain, nor do hyperkeratotic areas due to prolapse, similar areas due to syphilis, or desquamation of the upper layers of the epithelium. Schiller advocates scraping off the abnormal area with the sharp edge of a spoon and fixing and staining, but it is safer to excise the area with tissue on all sides of it. A positive Schiller reaction does not mean that cancer is present, but it does indicate abnormal changes in the cervix, and these should be viewed with the microscope.

The colposcope of Hinselmann is also of great value, not so much for the actual discovery of early cancer as for showing the operator what the cervical epithelium looks like. Once the examiner learns the appearance of the normal cervix, he begins to see abnormal areas and recognizes some of them as due to infection, cysts, exposed ducts and so forth. He also recognizes areas of ulcerated or hypertrophied epithelium divided by fine lines into squares and takes biopsy specimens from them. The use of Schiller's iodine solution in conjunction with the colposcope further demonstrates abnormal cervical epithelium. It has never been my good fortune with either of these tests to find a cancer of the cervix that had not been suspected, yet the amount of information obtained from the study of the cervix by these methods has been enormous and no doubt contributes to one's ability to recognize early, suspicious areas of cervical epithelium. Certainly the constant use of these two methods is of extreme value to the examining physician.

The diagnosis of cancer of the cervix by means of the stained vaginal smear was first introduced by Papanicolaou and Traut.¹ Their work was substantiated by the investigation of Meigs, Graham, Fremont-Smith, Kapnick and Rawson.¹⁹ There is no doubt of the value of this method, and the percentage of correct diagnosis is extremely high. A positive smear usually results in a correct diagnosis, but a negative one means little; the latter is comparable to the negative Wassermann reaction, which does not mean that syphilis is not present.

The apparently false-positive smear has yet to be proved. To do this would mean taking out the whole uterus and cutting serial sections along its entire length. The positive smear, in the absence of obvious cancer, may be a means of detecting extremely early growths. This part of the research has not been concluded. It is also possible to differentiate cancer of the endometrium from cancer of the cervix by the smear. A description of the method of taking the smears, the fixing and staining and the interpretation of results is given by the authors mentioned above. This method of diagnosis constitutes an epochal advance, and with Schiller's iodine and the use of the colposcope should aid early diagnosis. Possibly every woman over the age of thirty should have routine vaginal smears done once or twice a year, and be checked by the Schiller test and the colposcope at least once a year. A positive smear means that an investigation should be carried out under anesthesia. The uterus should be dilated and curetted and specimens of the cervix removed for microscopic section.

Biopsy. Study of the cervix by means of biopsy is the most important of the diagnostic aids. The specimen should be taken with supposedly healthy tissue on all sides of it. This is not always possible in the office, but it can always be done under an anesthetic. The disadvantage of the biopsy is that it can be negative and yet cancer can be present in the cervix. To be sure that it is not present, nearly all the cervical tissue would have to be removed. By means of the iodine test and the colposcope the most suspicious area can be demonstrated and biopsied.

CLASSIFICATION

The subject of classification is not necessarily included in a discussion of progress, but unless a single classification is universally agreed on, results and treatment cannot be compared. Comparison of the results in various clinics is at best inaccurate, but with different methods of classification adopted it is rendered even more so.

It is essential that tumors be classified, for certain clinics have a greater preponderance of early cases than do others. Cancer hospitals where patients can remain for treatment usually have larger numbers of advanced cases than do general hospitals. Since the League of Nations classification²⁰ is being universally accepted as the proper one, it is being favored more and more by American clinics. This classification is more complicated than the earlier one of the American College of Surgeons or the Schmitz²¹ method, and is not a great improvement.

The microscopic grading of the actual tumors is based on the individual ideas of the pathologist, and each one teaches his associates and students accordingly. It is doubtful whether there ever will be a standard method of grading tumors, but the

Martzlöff^{22, 23} method is to be recommended. His cases are grouped as those with spinal cells or low-grade malignancy, those with transitional cells or medium-grade malignancy, those with fat spindle cells or high-grade malignancy and those with adenocarcinoma. If Martzlöff's method could be used everywhere, great knowledge would accrue, but that it will ever become universal is unlikely.

Chambers²⁴ reports that in his attempt to grade 728 cases, 228 could not be classified because of insufficient tissue. Ten per cent were adenocarcinoma. Of the entire series, 15 per cent were Grade I, 9 per cent Grade II, 54 per cent Grade III and 22 per cent Grade IV — with extremely rapid growth. Chambers finds some indication that the more undifferentiated growths are frequent in youth and that there is no relation between the duration of symptoms and the extent of the disease, and states that most growths involving the cervix alone were cured without respect to their grade. Wetterdal²⁵ finds the percentage of cures of different grades to be so similar that the microscopic appearance of the cancer is of no apparent prognostic value.

Cancer of the cervix in gross may be of the cauliflower type and evverting, or ulcerating and inverting. It may involve the entire endocervix without breaking the mucous membrane of the cervix. It may appear early and yet involve the pericervical tissues and even extend laterally to the pelvic walls. It may be early and appear to be localized and yet have metastasized widely. It may produce enormous growth into the vagina and yet have a favorable prognosis, no extension having occurred into the vagina or pelvis.

Microscopically, cancer of the cervix is usually squamous-celled or epidermoid. About 6 per cent of the tumors are adenocarcinomas according to nearly all authors, and the results either with combined radium and x-ray or with surgery are the same as those in the epidermoid types. All tumors of the endocervix are by no means adenocarcinomas; most of them are epidermoid or squamous, the tumor probably arising from areas of embryologic squamous epithelium resting in the endocervix or from areas of metaplasia. Simpson, Thibaudeau and Burke²⁶ say that the ratio of adenocarcinoma to squamous-cell carcinoma is 1:26. Incidentally, 20 patients (32 per cent) of their 63 patients with adenocarcinoma were nulliparous.

TREATMENT

In a paper such as this it is not pertinent to go into the details of treatment used by each clinic. The references will guide anyone interested to the proper papers related to the subject.

Some clinics prefer to use radium alone in the treatment of this disease. The radium is applied in the canal of the cervix, against the cervix, against the sides of the cervix in the vaginal vaults, in square

boxes or colpostats, interstitially by means of glass, gold or platinum seeds, or interstitially by means of platinum needles ranging in strength from 1 to 50 mg. The radium in some clinics is in the form of radon; in others, the platinum-encased salt is used. Certain operators prefer a small amount for a large number of hours; others prefer a large amount for a small number of hours. Some space the treatments four days, seven days or two weeks or more apart.

The use of x-ray treatment is much commoner than formerly, and some clinics employ it as an adjunct to radium, giving it when it is thought that the broad-ligament extensions are not being treated satisfactorily, whereas others use it as an integral part of the treatment. In the latter group it is given either before or after radium treatment. Some surgeons give radium first, then x-rays and then radium again. X-ray treatment is adopted either in an attempt to destroy cancer in the pericervical tissues or broad ligaments and lymph nodes, or to cause cicatrization of the lymphatics of the broad ligaments and destroy lymph-node extensions.

There are many combinations of treatment, and without doubt in every clinic at some time every possible combination has been used. It is interesting that out of the wealth of experience no one method of treatment has been so satisfactory that it has been universally adopted. Apparently, any well-applied treatment that gives radiation in lethal doses to the entire tumor and its surrounding tissue is all that is necessary, and this may be accomplished in a great many ways. It is almost universally agreed that x-ray treatment cannot destroy cervical cancer in lymph nodes. Thus, surgical removal is necessary, but in most clinics it is not used. Bonney²⁷ writes:

I have on many occasions, at the close of the operation, discovered an infiltrated gland or mass of infiltrated cellular tissue so adherent to the great vessels as to be irremovable. All of the patients were treated by x-ray, but in spite of a definite target to aim at not one was saved.

The use of x-ray treatment to reduce the size of the cervical growth and cicatrize the broad ligaments, and perhaps to destroy cancer in the lymphatics, is proper. There are those who use x-rays to cross-fire the cervix, hoping to aid the radium in its action, and there are others who direct them straight through the pelvis to injure or destroy the growth lateral to the cervix. All methods are helpful, but no single correct one has been evolved. One of the most important functions of the roentgenologist is to direct the rays at the tumor; yet in many institutions the aiming is left to x-ray technicians. This is a weak point of roentgenologic treatment. From observation of patients treated by x-ray in the early days, it is obvious that the treatment was directed much too high, as evidenced by telangiectases.

The addition to the x-ray armament of the 500,000-volt and 1,000,000-volt machines may or may not be a distinct advance. A sufficient number

of cases over a sufficient number of years to allow any positive statement have not been reported. It is the opinion of the surgeons attending the clinic at the Massachusetts General Hospital that we have not yet learned how to use the 1,000,000-volt machine to the best advantage, and that it well may be that through trial and error we shall hit on the proper dosage. It is our opinion that at times this machine performs wonders, but so does the 200,000-volt machine. It is too early to know what voltage is best.

Merritt²⁸ advocates the use of the vaginal cone in administering x-ray treatment to the cervix. This is done through Ferguson speculums, and a total dosage as high as 6000r may be given. This method may have value, and further reports of its results will be eagerly awaited. So far, Merritt has treated 112 patients. He believes that his results are better than those attained with many additional portals and with radium alone.

To sum up, x-ray and radium alone or in combination usually destroy cancer involving the cervix, the cervix and vagina, and the cervix, vagina and pericervical tissue, if it is not in the lymph nodes. Yet there are certain radioresistant tumors that they cannot destroy. Furthermore, a satisfactory destructive dose cannot be given in the advanced stages of the disease without also destroying the bladder and rectum and other important organs.

In 1933, Leveuf, Herrenschmidt and Godard²⁹ advocated the removal of nodes in pelvic cancer, believing that although cancer of the cervix can be cured by x-ray treatment, lymph-node extensions cannot. In 1934, Taussig³⁰ first reported the results of dissections of the lymph nodes in a group of patients who had node extension as felt by pelvic examination (Stage II, League of Nations classification). His dissection was done before, during or after radiation, depending on when the patient was admitted to the hospital. Taussig believes that combined radium and x-ray treatment will cure the local disease but that surgery must be employed to cure lymph-node extensions.

I had the privilege of seeing the late Dr. Taussig operate and watched his meticulous dissection of the lymph nodes and lymph chains in the region of the common iliac artery, that of the external iliac artery and vein, that of the internal iliac or hypogastric artery and that of the obturator foramen and its nerve. Some of the nodes were not over 1 mm. in diameter, yet cancer was found in them, whereas in some of the larger ones no cancer was found. Taussig at times found it necessary to resect the external iliac vein during his operation. The only area that to an observer was not satisfactorily cared for was that near the ureter, and there it would have been necessary to tie off both uterine arteries to do a proper dissection. Taussig believed that combined radium and x-ray treatment was satisfactory for this area. As reported in his last paper,³¹

he operated on 175 patients with a mortality of only 2 per cent. Of 70 patients in Class II of the League of Nations classification, 37 per cent were living and well after five years. In a parallel group of 118 patients treated by radiation alone, the five-year salvage was only 23 per cent. In other words, Taussig demonstrated a 68 per cent greater salvage if lymph-node dissection was added to radiation. In 27 per cent of his cases cancer was present in the lymph nodes; 21 per cent of these patients were well after five years. If their treatment had been left to radiation alone, probably none would have survived.

Because combined radium and x-ray treatment has failed to be more successful, because of the damage that can be done with radium, because of Bonney's and Taussig's success in dealing with the lymph-node problem, and even more because of Lynch's³² work, which showed viable cancer in the cervix after satisfactory radiation, the question whether the radical or Wertheim-Clark operation should be revived is pertinent. Bonney in England and Lynch and Morton³³ in California advocate radical surgery, and I have now joined them. Bonney has operated on 500 patients with a mortality of over 9 per cent. He has treated advanced cases and has had to resect veins, arteries, the bladder and the bowel, and has attacked any cases that he thought he could possibly handle. It is difficult to compare his results with those following any form of radiation treatment, but they are excellent. It is obvious that before the operation can be universally adopted the mortality must be lowered. Bonney has kept 40 per cent of his patients well for five years, but he could not operate on all cases. Of his 500 patients, 300 had normal lymph nodes and 200 had cancerous nodes. His ability to cure lymph-node extension is the same as Taussig's, about 22 per cent of his patients surviving for five years.

It occurred to me after reading the reports of Bonney and Lynch and seeing Taussig's work that in selected good-risk patients the radical surgical operation could be done with less mortality and perhaps with as good results as those of radiation, and with a chance to cure certain patients with lymph-node extensions. The operation has been carried out in 57 cases; the mortality was zero, but the incidence of injury to the ureter was unexpectedly high — 10 per cent. The lymph nodes were involved in 16 per cent of the cases. The results indicate, however, that a judicious selection of patients for x-ray, radium or surgical treatment is going on that may lead to new heights of curability. The acme of radiation therapy has not been reached, but it can certainly do no harm to operate on patients with radioresistant tumors and those with involved lymph nodes, especially since the mortality can be kept low.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

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CASE 30191

DIFFERENTIAL DIAGNOSIS

DR. MERRILL C. SOSMANT†: If you do not object, I should like to reverse the usual order of procedure. Having been invited "downtown," I assume that the x-ray plays an important part in the diagnosis of this case. So I think that it is fair to start with the films alone without knowing anything about the history and see how far we can go by study of them. That is what I did with these films, which were sent to me the day before yesterday — I went over them thoroughly before I saw the history. It is not a completely honest or unbiased opinion because the roentgenologist knows simply from the way the films have been taken what they were thinking about; but perhaps it is as honest as any roentgenologist can be. Now let us look at the x-ray films.

The lungs are clear — no sign of tuberculosis or tumor so far as I can see. With clear lungs like that we can disregard the rales and rhonchi that come up later. The left half of the diaphragm is elevated. That is the only abnormality that I see in the chest film. The heart is normal in size and shape. Nearly all patients suffering from heart failure have an enlarged heart. The two exceptions are angina pectoris, where the heart may be normal in size and shape, and Addison's disease, where the heart is smaller than usual.

The next three roentgenograms are plain films of the abdomen. One was taken face up, the second face down, and the third upright. They all show a mass in the left flank about 15 cm. in length and 12 cm. in width (Fig. 1). It is smoothly outlined with a peculiar pattern of air in its center. Apparently there is large bowel here, close under the left diaphragm, which rules out an enlarged spleen, since the colon is usually below it. Here is a large, irregular collection of air, which we must consider later. The upright film shows several fluid levels, but no evidence of obstruction. There is a mass in the flank, and the first consideration is the left kidney. Starting out with an intravenous pyelogram, according to the dates we have here, both renal pelves are perfectly normal, so the mass is obviously not part of the left kidney. The ureters are also normal, with no evidence of obstruction. The bladder is well filled, also normal.

We have a large mass then, presumably with a necrotic center, in the left flank, and it is not kidney. Furthermore, the retroperitoneal shadows and the kidney shadow itself, as well as the iliopsoas shadow,

*On leave of absence.

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stand out quite well, so presumably it is not a retroperitoneal mass or it would displace the kidney more

The next x-ray, according to the dates on these films, is a barium enema. I am a little confused concerning the exact sequence of events. You can help me out here, Dr. Robbins?

DR LAURENCE L. ROBBINS: The next thing actually done was not the barium enema, but a swallow of barium given at night, no films were taken and that explains why you see the collection of barium

mass and that leaves the small bowel as the point from which the barium enters the mass. There are numerous spot films, do they show the communication?

DR ROBBINS: No.

DR SOSMAN: Here is one that shows a mixture of fecal material and barium in the mass, as well as the small sausage shaped outline.

To summarize the x-ray films, we have a large tumor mass in the left flank that communicates with

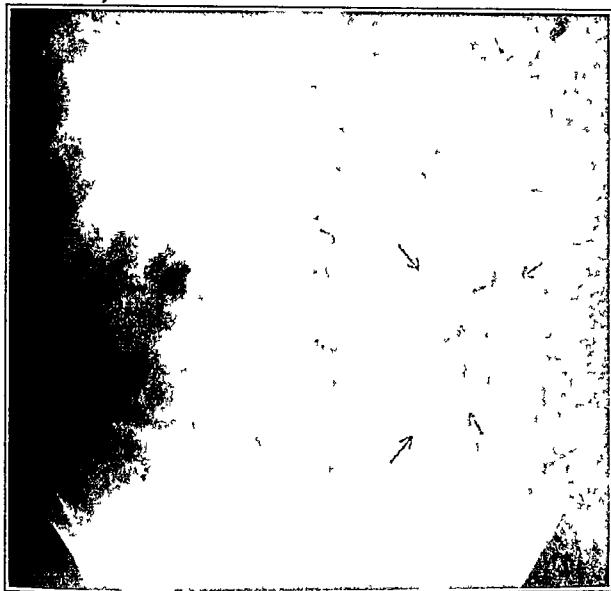


FIGURE 1 Plain Film Showing Mass with Air Filled Necrotic Center

overlying the distal transverse colon at the time of the barium enema.

DR SOSMAN: That is the thing I could not understand. Here is the barium enema outlining the colon, which looks perfectly normal. The descending colon is here, lateral to the mass, and above the mass in the transverse colon. But in the mass there is some barium, which looks as if it might have come through a communication from the descending colon to the center of this mass, but the explanation Dr. Robbins gave is satisfactory.

The next examination was a gastrointestinal series (fig. 2), and now we see this large irregular, tube-like collection of barium in the left flank, corresponding exactly to the air-filled shadow we saw a moment ago. That cavity in the mass communicates with the gastrointestinal tract, presumably not with the colon. The stomach is pushed upward over the

the small bowel and does not arise from the kidney. Presumably it is part of the small bowel itself, judging from the size and shape of this cavity here. There is no obstruction. It is in the left flank and is either part of the small bowel or directly connected with it.

Now let us go to the history and see if we can get any leads regarding what type of tumor mass it might be.

PRESENTATION OF CASE

A thirty-five year-old elevator operator entered the hospital because of pain in the left upper abdomen.

The history was rather unreliable and more or less contradictory. He was in apparent good health, except for an occasional stomach-ache relieved by soda, until two weeks before admission, when he

was seized by sharp pain in the left upper abdomen, which doubled him up. The pain lasted two or three days. Associated with the onset of his illness, or perhaps later, he developed chills and fever, marked anorexia and nausea. There was no vomiting. He had nocturia (one to three times), dysuria and urgency. He had two painful bowel movements with bloody stools during the week preceding admission. He apparently continued to work until the day of admission, when he had a recurrence of the severe

over the left costovertebral angle. Peristalsis was normal. The patient had pain in his abdomen when he coughed, but there was no rebound tenderness or masses. The prostate was of normal size, but boggy.

The blood pressure was 120 systolic, 75 diastolic. The temperature was 100.8°F., the pulse 76, and the respirations 16.

Examination of the blood showed a red-cell count of 3,500,000, with 65 per cent hemoglobin. The



FIGURE 2. Barium in Air-Filled Necrotic Mass.

pain in the left upper abdomen. No other information was available except that "he had lost a good bit of weight."

The patient broke his leg when he was seven years old, and at twenty-two he had a penile lesion.

Physical examination showed a well-developed, acutely ill, slightly stuporous man. A transient pleural friction rub was heard over the right apex anteriorly. There were a few fine basal rales on both sides, and occasional rhonchi at the right base. The left portion of the diaphragm was splinted. The heart was normal. There was marked tenderness and spasm in the entire left abdomen, most marked opposite the umbilicus and out toward the flank. Pain and tenderness were also elicited on percussion

white-cell count was 7400. The specific gravity of the urine was 1.006, with rare red and white cells in the sediment. The stools gave a +++ guaiac test. A blood Hinton test was negative. The blood nonprotein nitrogen was 21.5 mg. per 100 cc., and the protein 4.7 gm.; the chloride was 102 milliequiv. per liter.

A swallow of barium showed a normal esophagus. The stomach displayed a pressure defect and elongation. A small barium enema twenty-four hours later showed ready flow of the material to the cecum without delay. A large amount of gas and fecal matter was present, making the examination unsatisfactory. In the left upper quadrant a long, irregular mass of barium was seen, measuring 15

by 6 cm., which lay medial to the upper part of the descending colon and unattached to it. This apparently represented the barium swallowed twenty-four hours earlier. An intravenous pyelogram showed normal kidneys, ureters and bladder. There was a 15-cm. mass in the left midabdomen. Within the mass a large, air-containing, irregular cavity was seen. The fundus of the stomach was displaced to the left. A peculiar defect, thought to be due to an anatomic variation, was noted in the right ninth rib posteriorly. A gastrointestinal series showed a normal esophagus, but in the stomach there was a pressure defect, which seemed to be caused by a mass that lay behind and below it. This mass contained barium and apparently had no intimate connection with the stomach. The duodenum was normal, but the distal part was narrowed and displaced medially by the mass. It was thought that barium entered the tumor from the upper loop of the jejunum, but this was uncertain. The mass did not seem to cause obstruction. An x-ray film of the chest was negative except for increased density in the left lower lobe.

The patient's condition remained essentially the same. The temperature ranged between 100 and 103°F. Daily intravenous fluids and 2.5 gm. of sodium sulfadiazine were given. He had a moderate degree of rectal bleeding, but no vomiting. He was given two transfusions, and on the sixth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS (*Continued*)

DR. SOSMAN: There is a perfectly good possibility in a case like this that the histologic diagnosis could have been made from the stool, if the patient had been observant and had saved the specimen, since he may have passed some tumor. I assume that the chills and fever and the acute episode were due to the necrosis of the center of the tumor and subsequent discharge into the gastrointestinal tract. I do not believe that our medical students are taught to study the stools thoroughly enough. A great deal of information can be obtained from them. Only the pediatricians examine stools with great thoroughness.

The penile lesion brings up the possibility of gumma. A gumma in the gastrointestinal tract is extremely rare. I have seen two or three in the stomach. I do not believe that I have ever seen one in the small bowel or colon that was confirmed. Later on we find that the Hinton test was negative. It is an extremely sensitive test and it certainly should be positive if this were a gumma.

"There were few fine basal rales on both sides, and occasional rhonchi at the right base." These are the rales and the rhonchi that we threw away at the beginning of the exercise. We will leave them there.

Do the statements made in the abdominal examination mean that they did not feel a mass in the

left flank? The record seems to imply that tenderness and spasm had obscured the mass. The patient had a moderate anemia (3,500,000) and a normal white-cell count, and the urine was negative. The non-protein nitrogen was within normal range, and the blood protein was low.

I have already described most of the x-ray findings. The irregular mass containing barium, 15 by 6 cm. in size, which was apparently a false pocket in the tumor mass, I have described. I forgot to mention the small defect in the ninth rib posteriorly, but I think that is a congenital anomaly, sharp and clearly defined.

It is difficult at times to tell exactly where a fistula occurs. Barium runs around through the gastrointestinal tract with a great deal of variation or hesitation. It is sometimes impossible to say where the barium enters any given fistula or abnormal pocket. To sum the whole thing up, I think that this tumor mass in the left flank communicated with the bowel, in all probability with the small bowel. Then we have to try to line up all the various tumors that could occur in a thirty-five-year-old man with a very short history. Abscess, of course, is one of the first things to think of, but he was too young for diverticulitis. The usual diverticulitis of the colon occurs almost entirely beyond the age of fifty and is much commoner after sixty. There is no evidence of diverticulitis in the barium enema. If this man had been a farmer, or a man with similar occupational hazards, he would have been more likely to end up with actinomycosis. He had only a moderate fever, with a normal white-cell count, so that the diagnosis of abscess or inflammatory process is improbable. Tuberculosis is a possibility — a big broken down mass of tuberculous glands. It also would give more fever, and it is in the wrong location; usually it is in the right lower quadrant in the ileocecal region and frequently shows calcification, which I am unable to see in this particular case.

That leaves us, so far as I can think over the possibilities, with only a true neoplasm to consider — a neoplasm in a young man that had apparently developed rather rapidly. At least the patient had lost a good deal of weight, but the record does not say over what period of time. Neoplasm in a man of this age is usually sarcoma, arising in the bowel wall: a leiomyosarcoma, sometimes a lymphosarcoma or spindle-cell sarcoma or occasionally even an angiosarcoma. He passed a moderate amount of blood but had no extensive hemorrhage. We do not have to assume that this was a particularly vascular tumor. The red-cell count was only 3,500,000 — no marked anemia. Some authors have reported cases of melanotic sarcoma in the gastrointestinal tract, but the point of origin has always been doubtful. They are more probably metastatic from cutaneous melanomas. The carcinoids, rare tumors and are nearly apt to ulcerate. I throw

unusual possibilities. I should say that this belongs in the sarcoma group, probably originating in the small bowel, with an area of ulceration in the center of the tumor.

DR. BENJAMIN CASTLEMAN: Have you any preference among the sarcomas?

DR. SOSMAN: I have no preference. By taking the broader basis, I have more chance of being right. There is no reason to specify. Obviously it was a surgical problem, and the next thing to have been done was to explore the patient and see what could be done about it. The most we have done is to locate the lesion and to give an idea as to the type of tumor it might have been.

DR. CASTLEMAN: Are there any other suggestions?

DR. CHARLES G. MIXTER: Dr. Sosman ruled out the possibility of chronic or subacute abscess, the result of perforation, simply on the basis of the normal white-cell count and lack of fever.

DR. SOSMAN: That is true. An abscess in a man of this age is extremely rare. About the only reason for one would be perforation by a foreign body, such as a fishbone.

DR. MIXTER: That is what I was thinking about.

DR. SOSMAN: I have seen one in the spleen, — an abscess with a fishbone in the center of the abscess, — but this tumor mass had a thick wall, which I should not expect to see in pyogenic abscess.

May I ask how the X-ray Department interpreted the films?

DR. CASTLEMAN: They thought it was a malignant lymphoma.

DR. HORACE K. SOWLES: We discussed the case with Dr. Robbins the day before operation and came to about the same conclusion as that of Dr. Sosman, suggesting leiomyosarcoma or lymphoma as the most likely diagnosis. At the time of operation there was a large mass, involving the whole left abdomen, with a good deal of surrounding inflammatory reaction; it was bounded superiorly by the transverse colon and laterally by the descending colon and anteriorly was quite adherent to the anterior abdominal wall. In separating the anterior abdominal wall from this mass by finger dissection we went directly into an abscess cavity filled with mucopurulent material, and after a little more finger dissection, we brought up into the wound a loop of small bowel almost completely transected, with wide-open ends of small bowel, and tumor mass. It was possible, however, to isolate an afferent and efferent loop of the small bowel going into this area, to excise the wide-open portion, as well as a segment measuring 12 to 15 cm. on each side of it, and to do an end-to-end anastomosis of normal small bowel at that point. I did not see any particular object in trying to dissect farther, and I was afraid also that we might end up with a wide-open end of colon, which would not be easy to handle. We did the anastomosis, excised the area of small

bowel, put a drain in the lateral gutter through a stab wound and closed the incision.

CLINICAL DIAGNOSIS

Malignant lymphoma or leiomyosarcoma of small intestine.

DR. SOSMAN'S DIAGNOSIS

Sarcoma of small intestine.

ANATOMICAL DIAGNOSIS

Malignant lymphoma, lymphoblastic type, of small intestine.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The specimen we received contained a submucosal ulcerating tumor of the small intestine, about 3 or 4 cm. in length. It extended out into the mesentery of the small bowel as a extraluminal tumor mass measuring about 6 by 4 by 2 cm. Thus, a large extrinsic tumor and a smaller intrinsic one were present. On section they presented the uniform pinkish-gray smooth surface of lymphoma. Microscopically it proved to be of the lymphoblastic type, or what some prefer to call "lymphosarcoma."

DR. SOSMAN: Were there any palpable lymph nodes?

DR. CASTLEMAN: No nodes were found in the fat around the small bowel. It has been our experience that, in the majority of cases of malignant lymphoma of the stomach or intestine, the regional nodes are not involved.

DR. SOSMAN: That is the point I wanted to bring out: a solitary lesion in the gastrointestinal tract is susceptible of cure.

DR. CASTLEMAN: In cases of carcinoma we are likelier to find metastases.

DR. SOWLES: I might add that this man is reasonably sick. Postoperatively he had a certain amount of intra-abdominal infection and is probably going to develop a pelvic abscess, if he survives to that stage; of course, the prognosis is bad.

DR. CASTLEMAN: The prognosis of lymphoma of the gastrointestinal tract is fairly good if the tumor is completely removed surgically. It is only when the lymphoma has involved the lymph nodes that the outlook is bad.

DR. SOWLES: I doubt very much that we completely removed the tumor, although we did excise a goodly portion.

CASE 30192

PRESENTATION OF CASE

A fifty-four-year-old Italian waiter was admitted to the hospital complaining of epigastric pain.

The patient was apparently well until three months before admission, at which time he noted mild pain in the epigastrium, squeezing in character and coming on especially at night. It was inter-

mittent, lasting for a day or two and then disappearing for a week at a time. It was aggravated by meat and fried foods, and later by all solid foods; it was unaffected by the ingestion of milk or soda and somewhat relieved by bowel movements. About two weeks before entry into the hospital, the pain became much severer and almost continuous. It was associated with several bouts of chilly feelings and profuse sweating, occurring at night. On several occasions he was unable to retain fluid, which, after having apparently become caught at the level of the xiphoid process, was promptly regurgitated. There was no associated nausea. His bowel movements had been regular until he became constipated a few days before admission. He had lost 20 pounds of weight over a period of two months. He drank one pint of whisky a day until about five years previously.

Physical examination revealed a man complaining of abdominal pain but in no acute distress. The skin was soft, moist and warm. The tongue was heavily coated, and the breath foul. The lungs were clear. The heart sounds were distant. There was tenderness to deep pressure in the epigastrium, but no masses were palpable.

The blood pressure was 130 systolic, 90 diastolic. The temperature was 101°F., the pulse 108, and the respirations 20.

Examination of the blood revealed a red-cell count of 5,500,000, with 16 gm. of hemoglobin, and a white-cell count varying from 11,000 to 17,000, with 70 to 80 per cent neutrophils that showed a moderate shift to the left. The urine was negative. The stools were light brown and hard, they gave a +++ guaiac test on admission but subsequently became negative. The blood protein and non-protein nitrogen were within normal limits. The blood chloride was 98 milliequiv. per liter. Two bromsulfalein tests, at different times, showed 30 per cent and 15 per cent retention of dye after thirty minutes. A blood Hinton test was negative, as were a blood culture and tests for agglutinins against typhoid bacilli, *Brucella* and *Pasteurella tularensis*.

A gastrointestinal series revealed a 5-cm. area of esophageal narrowing above the cardia; the esophagus above this point was considerably dilated (Fig. 1). This area did not widen after the administration of amyl nitrite. Only a small amount of barium entered the stomach, and no defect could be demonstrated in the fundus. A barium enema revealed redundancy of the sigmoid. An esophagoscopy performed on the fifteenth hospital day revealed an area of reddening 4 cm. above the cardia. A biopsy of this area revealed acute and chronic inflammation, with epithelial hyperplasia and keratosis. Bougies (No 12 to No 24) were passed readily through the cardia, and subsequent x-ray examination revealed no residue in the esophagus, the barium passing readily into the stomach.

During his hospital stay the patient continued to complain of gnawing epigastric pain, which became severe on occasions. The temperature gradually rose to 103°F. At that time he appeared toxic, lethargic and somewhat incoherent. The pharynx was beefy red and two throat cultures revealed a few colonies of beta-hemolytic streptococci. Both leaves of the diaphragm were elevated. A pleural



FIGURE 1 Roentgenogram Showing Esophageal Dilatation

friction rub was heard over the right third rib anteriorly. A few sticky rales were audible at the right base, later replaced by numerous inspiratory and expiratory rales, associated with dullness and increased tactile and vocal fremitus. A roentgenogram of the chest revealed areas of density in the right lower and left upper lobes (Fig. 2). Because of the chest findings, sulfadiazine was administered in adequate dosage for an eight-day period, without apparent effect. The abdomen became increasingly distended, and the patient developed diarrhea alternating with periods of relative constipation.

Periods of elevation in temperature to 101 or 103°F. alternated with periods of almost normal

temperature. The chest condition showed improvement by physical and x-ray examination, but the patient remained lethargic and at times semistuporous, with only vague orientation regarding time and place. Neurologic examination revealed small irregular pupils that reacted sluggishly to light. The fundi were normal. Muscular coordination was poor. The abdominal and cremasteric reflexes were absent, and the deep tendon reflexes depressed. Vibration sense was diminished

dominal pain, also associated with shock. The pain was relieved by morphine and atropine, but the patient expired forty minutes later.

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM B. BREED: I am sorry that I have so little time, because I had planned a nice wordy discussion of this case to cover up various spots of ignorance, and as you all know, the length of the discussion is inversely proportional to the accuracy.

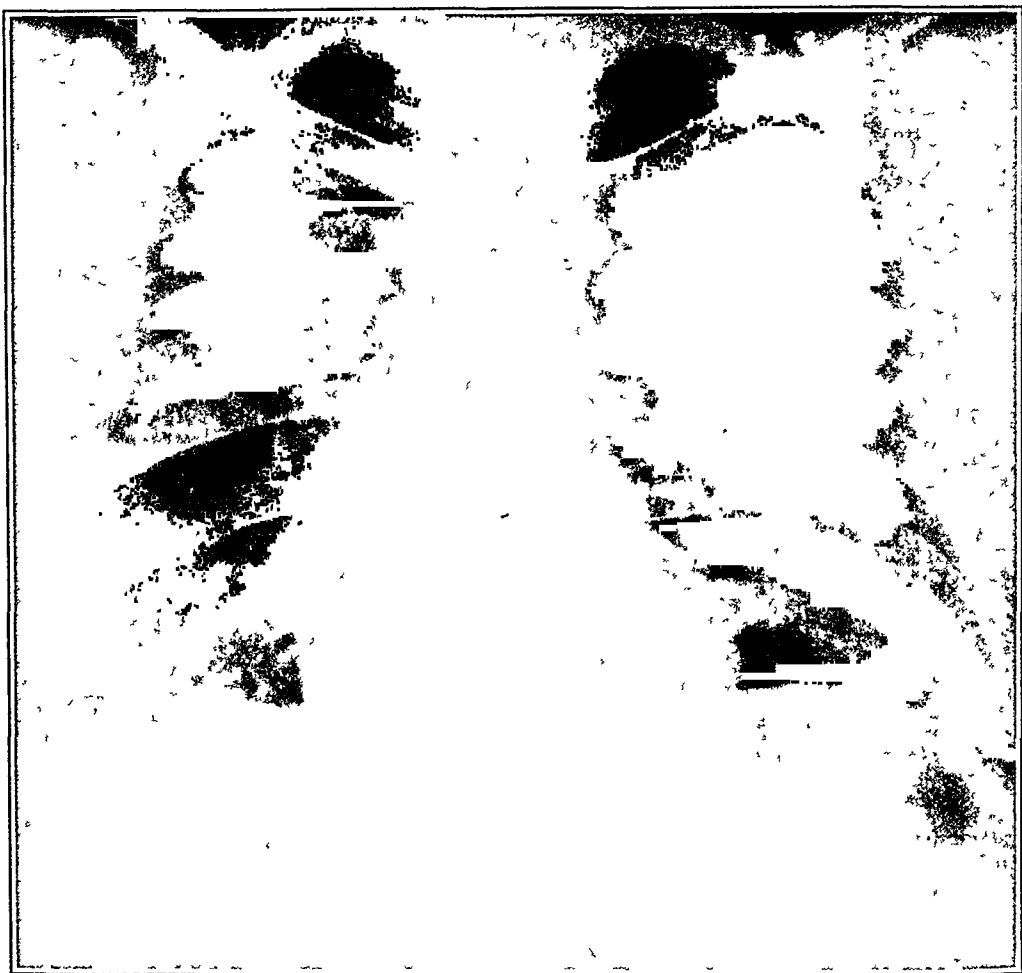


FIGURE 2 [Roentgenogram of the Chest Showing Areas of Density in the Right Lower Lung

in the lower extremities. On lumbar puncture the spinal fluid was clear, under normal pressure and free of cells; the total protein was 73 mg. per 100 cc. On the thirty-eighth hospital day the patient had an attack of sudden severe pain that caused him to sit up and writhe about the bed, clutching his epigastrium. He was pale and sweating, his lips and nails blue, his pulse feeble, and his blood pressure 60 systolic. The abdomen, however, remained soft. Within a few hours he returned to his usual state of lethargy. Four days later the stool was found to be tarry, and the guaiac test was + + + +. On the following day, his forty-third in the hospital, he suffered another severe attack of ab-

But now I am forced to gird my loins and be more accurate than I had planned. When one is given a case that involves so many different structures in the body, such as the esophagus, the lungs, some viscus presumably under the diaphragm and possibly the central nervous system, it is important to try to hit on one pathologic process that will account for all of them. Of course the granulomas, such as syphilis and tuberculosis, stand first on such a list. The patient had negative blood Wassermann and Hinton tests, and also a spinal fluid that appears to have been negative. I am going to get, I hope, some information from Dr. Robbins. Perhaps he will help clarify the chest

situation, which is quite hopeless to my mind. In trying to explain these widespread lesions, the well known standby of lymphoma comes into prominence.

I shall talk to Dr Robbins about the x-ray films, or perhaps I shall just listen.

Dr LAURENCE L. ROBBINS: This is the chest film showing areas of increased density scattered throughout the right lower lung field, with a few in the left lung. I do not know the answer in this case, but I think that the patient had some reason to have changes in the chest because of the obstruction in the esophagus.

Dr BREED: This report is a little contradictory, since it says, "A roentgenogram of the chest revealed areas of density in the right lower and left upper lobes."

Dr ROBBINS: I did not put up the lateral film in which there are a few areas of increased density in the left upper lobe.

The esophagus is dilated, as one can see from this film. Without any question the process was of considerable standing because, in addition to the size, there were fluid and food in the esophagus. This other film was taken later, after the bougienage, when there was no delay at the cardia. When I examined him the lower esophagus seemed to be funnel shaped and looked like cardiospasm to a certain extent. The esophagus did not change with amyl nitrite, and at no time could I be sure of a defect in the stomach, although I did raise the question on the chest film whether there might have been something wrong with the fundus.

Dr BREED: That does not look like a metastatic process in the lung?

Dr ROBBINS: It is not characteristic of it.

Dr BREED: I am a bit disturbed because the record says that there was esophageal narrowing 5 cm. above the cardia.

Dr ROBBINS: It is not particularly clear in these films, but if this is the cardia there is an area of narrowing about 5 cm. above it.

Dr BREED: Did you call it cardiospasm?

Dr ROBBINS: I raised that question and the other alternative that one always worries about in that area.

Dr BREED: Dr Edward B. Benedict apparently esophagoscoped this man, found a red mucosa and did a biopsy, which showed acute and chronic inflammation with epithelial hyperplasia and keratosis.

What does that mean to you, Dr Castleman?

Dr BENJAMIN CASTLEMAN: Only that there was some keratosis, which could have been the result of chronic inflammation.

Dr BREED: I think it is extremely unlikely that one diagnosis can explain the findings in the esophagus and the presumable lesion underneath the diaphragm, and I doubt that the correct diagnosis will be even mentioned before Dr Castleman tells us about it.

Certainly the patient had a reasonably rapid and progressive toxic or septic process, with fever and epigastric pain, but with no obvious peritoneal irritation. On examination during all this time, his abdomen was said to have been soft. There was deep tenderness, which is not to my mind particularly significant. Looking at these x-ray films now, I think that this process could perfectly well have been a reflection of some sort of disease under the diaphragm.

Let us assume that the patient had cardiospasm or some other benign constriction of the esophagus above the cardia that was dilatable with bougies. I am going to assume that without going into detail, and I also believe that his main difficulty was under the diaphragm in the region of the liver. He had had a certain amount of alcohol for thirty years, and he exhibited some evidence of liver dysfunction. Possibly he had a hepatoma in a cirrhotic liver. Let us see if that adds up to anything. That would explain a good many of the symptoms. It would also explain, I believe, the lesions above the right diaphragm. It would not account for his sudden death, which I am unable to explain. The story gives one the impression of a ruptured vessel without any evidence of peritoneal irritation. On examination, this seems to be an unlikely explanation. A subdiaphragmatic abscess or abscess in the liver, amebic or otherwise, might explain the picture. I believe that the neurologic findings were probably terminal and that he did not have actual disease of the nervous system. Certainly nothing of that nature is demonstrable in the record, and the findings on physical examination could have been preterminal.

In trying to arrive at a diagnosis it is a great mistake to guess too much. I am prepared, however, neither to make a diagnosis nor to guess the diagnosis. I merely say that I think the primary lesion was probably in or about the liver and that it probably was some sort of malignant process, not primarily one of infection—a hepatoma in a mildly cirrhotic liver is all right, but it is pure guesswork. One could name three or four different mortal diseases of a malignant nature, but I am not prepared to guess.

Do you want me to be more specific?

Dr CASTLEMAN: Yes.

Dr BREED: Do you want me to make one diagnosis?

Dr CASTLEMAN: That would be preferable.

Dr BREED: It would be pure guess, and I am not sure it is legitimate. Did he have one or two diseases? Is that a fair question?

Dr CASTLEMAN: Not exactly, but I am willing to say that he had two diseases that were related.

Dr BREED: Since I am pushed into a corner and have to guess, I shall say that he had a hepatoma secondary to a cirrhotic liver.

Dr EARLE M. CHAPMAN: I secretly enjoyed Dr Breed's sweating. He was in exactly the same posi-

tion that I was in. I was completely puzzled and could not make a diagnosis. Dr. Paul D. White, who was previously on service, thought of a number of possibilities; and he, too, was wrong. Dr. Gerardo M. Balboni, who had been taking care of the patient for a long time, was convinced that he had Korsakoff's disease, with cirrhosis of the liver. We did not have much else to go on. Dr. Breed was astute in placing the disease below the diaphragm because Dr. Balboni and I put it above.

DR. BREED: But he died, do not forget that.

DR. CHAPMAN: He was going down hill so fast that we asked the Surgical Service to see him; they declared that he did not have a surgical abdomen.

of the symptoms. It could also explain the agonizing abdominal pain with death within a few hours.

DR. BREED: You would not be willing to accept cirrhosis alone in this picture?

DR. JONES: So far as the pain and fever are concerned, yes; but I do not believe that cirrhosis was the whole or the true story.

The difficulty in swallowing is the other curious part of the story. One thing might be mentioned in defense of Dr. Benedict, who did the biopsy. It is frequently impossible to obtain an adequate specimen by esophagoscopy, owing to the presence of an area of inflammation just above the actual site of trouble, which may be carcinoma. Dr.



FIGURE 3.

At the first attack that is described he had pain. Dr. Madelaine Brown examined him neurologically, and during this examination he had a convulsive-like seizure, which was extremely dramatic. Five minutes later he was in shock, holding his abdomen and writhing in pain. We did not know what was wrong with him. He survived that attack, but died in a subsequent attack five days later.

DR. CASTLEMAN: Dr. Jones, have you any suggestions to offer?

DR. CHESTER M. JONES: I am sure that I cannot make a diagnosis, but from the facts given us there are certain things one has a right to mention.

In the first place one sees, although infrequently, acute abdominal pain with cirrhosis of the liver—so acute that the question of surgical intervention arises and severe enough to require morphine, a drug that can precipitate a fatal outcome. It is perfectly fair to suspect that this man may have had cirrhosis of the liver. That would account for a great many

Robbins also had to hedge on the x-ray interpretation of cardiospasm. The diagnosis of carcinoma ought to be seriously considered, and I gather that Dr. Robbins did consider it as a possibility.

Two other points are worthy of mention: the patient had evidence of a hepatic disorder and he was an Italian who had used a reasonable amount of alcohol. Cirrhosis is not an uncommon finding in this particular group. In addition, there was some dye retention, which bears out that possibility.

The bleeding is also interesting and has not been explained. It is quite possible that the patient had a carcinomatous lesion from which he was bleeding, or he might even have had varicosities just below the cardia, rather than above, as a cause of bleeding.

The story of mental confusion and the neurologic findings,—the absent reflexes and the diminished vibration sense,—the very red, sore mouth—which was certainly not due to a streptococcal infection—and the clear spinal fluid with definite ele-

vation in protein, all could go with deficiency disease. This would fit in with a Korsakoff's syndrome.

I think Dr. Breed is absolutely correct in refusing to be drawn into a flat diagnosis. He has shown good judgment. But I believe that cirrhosis was in the background and that there might have been a malignant process in addition, superimposed or adjacent to it.

CLINICAL DIAGNOSES

Alcoholic cirrhosis of liver?

Korsakoff's psychosis.

Carcinoma of stomach?

DR. BREED'S DIAGNOSIS

Cirrhosis of liver, with superimposed hepatoma.

ANATOMICAL DIAGNOSES

Epidermoid carcinoma (Grade III), of esophagus, with metastases to mediastinal and retroperitoneal lymph nodes, pancreas and esophagus.

Perforation of pancreatic metastasis into cardiac end of stomach.

Massive hemorrhage into stomach.

Lipid pneumonia.

Multiple foci of degeneration in cerebral cortex.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy on this man showed a large mass in the abdomen that apparently invaded, or was part of, the body and tail of the pancreas; this mass had perforated into the stomach (Fig. 3). At the time of the autopsy we thought that that was the whole story. The stomach was filled with a huge cast of clotted blood.

Later, however, in the esophagus, 5 or 6 cm. above the cardia, we found an ulcerated lesion measuring 3 by 2 cm. that had infiltrated the wall; about 2 cm. above that was a similar but smaller lesion, and there was a third one above that. These three esophageal lesions, as well as the mass in the abdomen, proved to be epidermoid carcinoma. The tumor was therefore primary in the esophagus and not in the pancreas, and the "pancreatic mass" proved to be a large group of cancerous retroperitoneal lymph nodes that had invaded and replaced the body and tail of the pancreas.

That does not explain the lesions in the lung, which, grossly, were moderately firm and believed to be carcinomatous metastases. These proved to be areas of oil-aspiration pneumonia or lipid pneumonia, which is often found in patients with cardio-spasm or other lesions in the esophagus. The man had probably been taking a lot of mineral oil, and during the course of time appreciable amounts of oil had gained access to the lungs.

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NEW MEDICAL FOOD REGULATIONS

A POINT system of food rationing has now been in operation for well over a year, having been inaugurated on March 1, 1943. The fact that our nation continues to eat, and to eat moderately well in addition to supplying foods to other countries, seems to indicate that the system works in a reasonably satisfactory manner. It has its faults and its inadequacies; abuses have crept in and black markets have flourished, human nature being what it is, yet we have kept ourselves not only free from want, but well nourished.

On account of the obvious need for special dietary consideration on the part of certain institutions and

population groups, the director of the War Food Administration requested the National Research Council in April, 1943, to appoint a committee of physicians to advise concerning the extent of these special needs and the best method of meeting them. The Subcommittee on Medical Food Requirements, within the Division of Medical Science of the National Research Council, under the chairmanship of Dr. William D. Stroud, of Philadelphia, resulted, and its recommendations were published in the October 16 and 23, 1943, issues of the *Journal of the American Medical Association*.

As of April 6, 1944, thirteen months and six days after the inauguration of point rationing, the Office of Price Administration adopted the recommendations of the subcommittee, practically without change! For over a year each local board, each state and each region have solved their own food-rationing problems as they apply to the care of the sick, and in many instances have devised their own more or less complex, more or less satisfactory systems of operation. The mills of the gods certainly grind exceeding slow, whatever the quality of their meal.

In June, 1943, at the request of the District Rationing Officer, the president of the Massachusetts Medical Society appointed an advisory committee to aid in the medical aspects of food rationing. The Boston district, which originally extended westward to Worcester, was enlarged in October to include the entire state, and during the winter was merged with the New England Regional Office, by some sort of phagocytic process. There has been a tendency, consequently, to enlarge the usefulness of the Massachusetts committee, since Rhode Island is so far the only other New England state with a medical advisory committee.

The new regulations, adopted at long last by the Office of Price Administration, are more drastic than the homespun principles under which the district has functioned for nearly a year. The list of diseases that automatically rate extra rations is a short one, consisting only of diabetes mellitus, active tuberculosis, chronic nephritis of the nephrotic type, cirrhosis of the liver, severe hepatitis, chronic suppurative diseases, severe burns, gastrointestinal lesions and pregnancy for extra meats, fats and oils, and diabetes and active tuberculosis for extra allot-

ments of processed foods. All other requests must be approved by the New England Regional Office — an extra hazard for those physicians who still ask additional allotments for their patients with gall-bladder disease, heart conditions of all types, obesity, anemia, pneumonia and polyneuritis.

Furthermore, with the recent lowering of point values and the virtual abandonment of rationing for many foods, it seems likely that little will be needed for anyone in the nature of extra concessions.

FREDERICK II OF HOHENSTAUFEN AND HIS FAVORITE SPORT

A CULTURED, gifted, thirteenth-century pioneer in medical education and economics, a fighting king, the founder of the University of Naples in 1224 (the first school in Europe to be established by a charter), a student of mathematics, natural history and philosophy, a man with an absorbing passion for the now nearly extinct sport of falconry and the writer of a book on the subject, composed in the critical spirit of modern science — such was Frederick II of Hohenstaufen, Holy Roman Emperor, King of Sicily and Jerusalem.

His treatise on falconry is one of the most important zoological works of the Middle Ages. The original text, compiled by himself, was lost in a battle before Parma, but a devoted son, Manfred, prepared a revision of the first two books, the basis for the printed editions that followed. Fortunately at least six other contemporary manuscripts of the complete work are known, and six more of the two-book manuscript. There have been four printed editions of the first two books, but none of the entire work until the one recently issued by the late American ophthalmologist, Dr. Casey A. Wood, and his secretary, F. Marjorie Fyfe.¹ After his retirement from practice in Chicago, Wood spent years in Europe probing into and comparing the texts of every manuscript of this book that he could find.² In the University Library at Bologna he discovered the fullest text, and in the Vatican Library at Rome the one most superbly illustrated. Wood's translation covers over four hundred large pages, an indication of how detailed was the study of Frederick II. The king recorded for the first time such observations as the pneumaticity of the bones, the form of

the sternum, the mechanical condition of flight, and migrations. Frederick experimented on the artificial incubation of eggs. The scientific world owes much to Wood for his clear rendering of the Latin manuscripts. By publishing the whole work, much new material has been added, particularly on the use of the lure, on the training of falcons in a cast, on crane hawking with gyrfalcons, on heron hawking with sakers and on hawking at the brook with the peregrine falcon.

To Wood's translation of *De Arte Venandi cum Avibus*, Walter Schlüter has added a chapter on falconry in modern times. Falconry was a favorite sport of all classes in Europe up to the time of the French Revolution. It has survived in a few areas. In England there are examples of family falconers running through many generations, such as the Fleming family of Barochan Tower, who, up to recent years, were still flying falcons in England and in India. Holland, France, Germany, Australia and America all have small but active centers of falconry, but the great days, when Frederick II had hunting lodges scattered throughout the mountains of Sicily and southern Italy, in places all too familiar today in our daily news, are long past.

Frederick has other claims to fame besides his scientific book on falconry. He gave to Sicily a remarkable code of laws, promulgating a regulation of the practice of medicine, the first elaborate work of its kind. To Salerno, the great medical school of his day, he granted the exclusive right to confer the license to practice medicine in the whole kingdom, and his stipulation for the length of medical studies has a modern ring: five years, plus one year of practical work under the guidance of an experienced physician, corresponding to one year of internship. A second postgraduate year was taken by surgeons, similar to a residency. Are we less wise than Frederick II in curtailing medical education in wartime, whereas, he, who lived in a continuous state of war, provided five or six years for medical training? Possibly the twentieth century has something to learn from the thirteenth.

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MASSACHUSETTS MEDICAL SOCIETY

DEATH

PARLOW — George G. Parlow, M.D., of Wareham, died April 20. He was in his seventy-fifth year.

Dr. Parlow received his degree from the College of Physicians and Surgeons, Boston, in 1905. He was a member of the Massachusetts Medical Society and the American Medical Association.

CORRESPONDENCE

AN EXPRESSION OF APPRECIATION

To the Editor: National Hospital Day is Friday, May 12. This year in bringing hospitals to the attention of the public, emphasis is being placed on what the hospitals are doing in keeping our civilian population well and at work during the third year of the war. We believe that we are making a vital contribution to the war effort, and that the public should be informed regarding some of the difficulties being encountered in the operation of our institutions.

The committee arranging for the observance of National Hospital Day in Massachusetts was unanimous in requesting that I express to the members of the Massachusetts Medical Society, through the *New England Journal of Medicine*, our very real appreciation of the contribution the doctors on our hospital staffs are making in keeping our hospitals operating. Many who had retired from active practice have come back to work long hours. The rest of the doctors have greatly increased their burdens in order to give adequate care to our communities. As president of the Massachusetts Hospital Association, in the name of the administrators of our hospitals, I wish to thank the members of the Massachusetts Medical Society for the invaluable contribution they are making to the continued operation of our institutions. Without their devoted service, it would be impossible to keep our doors open to the public.

GEORGE A. MACIVER, President
Massachusetts Hospital Association

BOARD OF REGISTRATION IN MEDICINE

To the Editor: Recently a member of the medical profession of Massachusetts was quoted by the newspapers as saying, in regard to certain matters concerning the Board of Registration in Medicine, that the Board had been "a sort of plague spot for years." The statement did not say what sort of plague spot nor how long it had been a plague spot, but the quotation went on to state that the conditions, however, had been improving. This also was not made clear and in view of the fact that the Governor had seen fit to "oust" three members of the Board, according to newspaper reports, one wonders in what the "improvement" had consisted. The situation has been left in a very unsatisfactory state. The Governor is reported to have said "the less said about it the better." The Attorney-General is reported to have said that he found no ground for criminal action. This may be taken to mean that there was no violation of the letter of the law.

I am writing because I think the medical profession and the public have a right to know more about the background of the situation and because I know nothing about the specific facts in the late incident, although I am familiar through years of experience with the work of the Board. Therefore, I write impersonally and I shall attempt to point out the framework of reference within which the discussion should take place.

The duties of the Board lie, in general, in two fields—the licensing and the unlicensing of physicians. The former is usually done after examination, although occasionally, in the case of a physician whose license had been revoked by the Board, without examination, but a license is revoked only after a hearing, as provided by law.

What qualifications does the law set for performing the first duty, which includes the setting of an examination that shall be practical in character and sufficiently thorough to test the qualification of the candidate for the practice of medicine? Substantially these: the candidate for appointment shall himself be licensed by the Board and shall be engaged in the practice of medicine for ten years, but he shall

not be connected with a medical school. This last phrase excludes from the Board the physicians who are likely to know how to set an examination and the examinations are, therefore, more likely to be an unsatisfactory test than if they were given by someone familiar with teaching. Is it going too far to say that the law sets a premium on not knowing how to set an examination?

What of the ten years of practice? Of what value is that? Probably it impairs the competence to set an examination, for the farther the candidate is from his own student days the less likely he is to be familiar with the technic of that procedure. But it is in the unlicensing of physicians that the ten years of experience in practice may be invaluable. The board member has had an opportunity to experience the problems met in actual practice and is in a better position to exercise discretion in deciding whether a physician has been guilty of "gross misconduct in the practice of his profession."

It would be interesting to go into the history of that disqualification—connection with a medical school—and find out why it was introduced into the law and why it has not been deleted when in the opinion of many persons it has no present usefulness and may actually prove to be an obstacle to attaining one of the purposes for which the Board exists. Thus the first difficulty is with the law.

The second difficulty is of a different character: not all governors take the Board seriously. Again and again physicians have been appointed to positions of trust, when consulting the records of the Board might have indicated the impropriety of the appointment. It is not a question of asking the Board or its chairman or its secretary for recommendation or disapproval. It is asking for the record, the facts. Has the candidate ever been reported to the Board for any alleged impropriety in practice, what was the nature of the complaint, and what were the findings of the Board?

Appointment to the Board carries an inconsiderable salary but for some physicians prestige is enhanced. Too often the appointment is in payment for some political debt or as a reward for medical services to the community (or to the executive) faithfully performed. The law says that the candidate shall have been engaged in practice for ten years, not for one hundred and ten years, and the candidate should be young enough to have vigor to carry through carefully and conscientiously what some persons may regard as the chore of evaluating and grading justly six, seven or eight hundred examination books each year. Although the work done at ten Board meetings a year may be of great importance, it is an incomparably lighter burden than properly grading the examination books. Rarely does the question seem to be asked, Has the candidate fitness for setting examinations, understanding, firmness, wisdom, integrity, a judicial mind?

At one time there were on the Board of Registration in Medicine in Massachusetts, two members who had had cerebral hemorrhage. The presumption was against these men being able to act with proper discrimination if subjected to stress, or in cases involving delicate weighing of evidence. This brings us to the third difficulty.

Under the statute, the Board may under certain circumstances exercise its discretion, which means that individual members must exercise their discretion. If the executive has appointed indiscreet persons, the system breaks down under pressure. In the nature of things stress is inevitable. By no possible effort can the procedure be made mechanical. On the one hand there are the welfare, happiness, and lives of the citizens of the Commonwealth, all human beings; on the other hand are candidates for licensure, eager for practice, with various degrees of qualification, also human beings. Judgment concerning qualification for practice requires a fine discrimination, a scalpel wielded with intelligent skill, not a blunderbuss fired in all directions.

The problems presented by the Board of Registration in Medicine are in part problems for the medical profession. The question that I should like to bring home to every physician in Massachusetts who is really interested in upholding the high ideals of the profession by trying to realize them is, What have you done to change conditions in this state so that no one can say with justice that we have in Massachusetts a plague spot?

STEPHEN RUSHMORE, M.D.

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Boston

(Notices on page xii)

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THE HISTORY OF THE DISCOVERY AND ISOLATION OF THE FEMALE SEX HORMONES

GERHARD J. NEWERLA, M.D.*

WALTHAM, MASSACHUSETTS

I SWEAR by Apollo, the physician, and Aesculapius, and Hygeia, and Panacea, and all the Gods and Goddesses . . . [that] I will not give a woman a pessary to cause abortion." Thus reads the Hippocratic Oath, to which every physician swears, and thus for the first time in medical ethics the Greeks recognized the sanctity of motherhood. Yet even in the Greek civilization of Hippocrates abortion was not illegal or criminal, but was merely left to the midwives, who also officiated at births and brought together suitable matrimonial candidates.

The phenomena of menstruation and pregnancy have been known to man as long as has the human race itself, but their true nature and mechanisms were not understood until fairly recent times. The word "menses" is indirectly derived from the Greek noun meaning "moon." The ancient Greeks used it to describe the monthly flow from the vagina. They regarded the menses as effect of the moon on the female organism and as a periodic cleansing of the uterus.

According to the *Ayurveda* by Susruta,¹ of India (ca. 1400 B.C.), the ancient Hindus regarded the menstrual flow as an "impurity" of the seven body elements. Impregnation was considered to be easiest during the menstrual flow, and the fetus was believed to be formed by the union of the male semen with the "fiery" menstrual blood. The sex of the fetus was presumably determined by the preponderance of either the semen, which produced a male fetus, or the menstrual blood, which produced a female one. If both elements were equivalent, a hermaphrodite was created. The Egyptians of the era of Ptolemy (ca. 300 B.C.) already knew means by which to induce conception and increase fertility, and could diagnose pregnancy at a comparatively early stage.¹

The true physiology of the ovaries, however, remained unknown until the seventeenth century. Theodore Kerckring² (1643-1693), of Amsterdam,

was one of the earliest to state that the "ovum" — as the ovarian follicle was then called — was expelled by the onset of menstruation or by sexual excitement. This view was disproved in 1843 by Ritchie,³ who demonstrated that menstruation and ovulation were dependent on each other and that ovulation determined menstruation. Yet it was not until 1927 that Corner⁴ proved that even menstruation may occur without ovulation. Hejdentrikk Overkamp⁵ (1651-1692), a contemporary of Kerckring, believed that the "ova" — that is, follicles — formed a substance that passed into the general circulation. The Frenchman Nicholas Venette⁶ (1633-1698) called this substance "the spermatc vapors" and believed that it produced menstruation after entering the systemic circulation. François Mauriceau⁷ (1637-1709) was the first to suggest that conception was not dependent on menstruation, and Bischoff⁸ in 1844 proved that the ova matured periodically and independently of coitus. The concept that the primary function of the uterus is pregnancy and that menstruation is merely an indication of the thwarting of this function is therefore of modern origin.

It is of historical interest to observe that some of the earliest indications of the variability of the abnormal female sex characteristics that today are recognized as embryologic or endocrine disorders were expressed in the artistic creations of ancient and medieval origin. At least two types of mixed-sex personalities can be detected in the classic sculptures and paintings: virilism and hermaphroditism. Antique statuary unearthed by excavations in Asia Minor, Greece and Italy show these two distinct types; for in those times it was the acme of sculptural endeavor to adorn men with feminine characteristics, and women with those of men. Perhaps the best-known example of virilism in women is the famous statue of Psyche, the mistress of Eros, now preserved in the Museum of Naples. This figure exhibits small and flat breasts on a wide masculine chest and a long body of straight lines terminating in a small pelvis. Hippocrates describes in his

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Epidemics two women with marked facial hirsutism during the menopause.⁹ Many artistic works and even modern side shows still attest to the prevalence of this curiosity. Archaeological research indicates that the inhabitants of the island of Cyprus in the eastern Mediterranean in antiquity worshiped a bearded female deity, part of a cult imported from the East, but no sculptures portraying this goddess have been unearthed.¹⁰

The hermaphroditic statues of the ancient Greeks were frequently sculptured after living models, but some were based on an ideal concept that, incorporated the most aesthetic features of both the male and the female bodies. The best examples of this natural hermaphrodite statuary are preserved in the Villa Albani in Rome, where the art-loving Cardinal Albani (1692-1779) assembled an exquisite collection during the eighteenth century; in the State Museum of Berlin; and among the art objects in the Museum of Naples, from those that were excavated at Herculaneum, the city destroyed together with Pompeii by the eruption of Vesuvius in 77 A.D. These hermaphrodites possess a predominantly female body contour adorned with male genitalia.

The best sculptures of natural hermaphrodites were unearthed in the Necropolis at Myrina in Asia Minor. These statuettes, which are of terra cotta, display composite characteristics of both young men and young women. They show a delicately rounded neck and generous fatty pads, especially on the buttocks, hips, thighs and pubes. The abdomen is slightly protruding, but the face shows a delicate and gracious feminine expression. The well-formed breasts appear small, and the extremely small external genitalia are those of the male.

The masters of the Renaissance likewise preferred females suggestive of hypogonadism. The portraits by Botticelli (1447-1515) depict women with small breasts, a long neck and long extremities, as in the paintings "Truth and Repentance" and "The Birth of Venus," now in the Art Galleries in Florence. A similar trend is seen in the Flemish brother-painters Van Eyck, who lived in the fifteenth century. Jan Van Eyck's "Eve" and "The Love Spell," by one of the pupils of the Van Eycks, now in the galleries of Leipzig, are examples of this trend. The Museo de Prado in Madrid has a painting of the crucifixion of the "bearded" Saint Wildegeforth. The Spanish master Ribera (1588-1652) portrayed himself together with Madelaine Ventura, also a bearded woman, who is shown nursing an infant.¹¹

Perhaps the earliest medical conception — or rather misconception — of the value of glandular products found its expression in organotherapy — that is, in the medicinal use of various animal and human tissues and excretions for the express purpose of deriving certain specific physiologic effects from their use. In fact, *materia medica*, and especially therapeutics and endocrinology, have sprung

from this type of remedial custom of primitive races and ancient civilizations. The primitive tribes had already observed how some animals — and among these even the herbivorous cow — swallowed the placenta after their young had been born. It was therefore logical to assume that placental tissue would arrest post-partum hemorrhages, stimulate milk secretion and even cure sterility. The long survival of primitive organotherapy was due primarily to popular superstition and a belief in magic powers, and had no scientific basis. One reads today with amazement of such customs as eating one's enemies or the organs of certain animals to acquire their particular qualities.

The rationale of medieval substitution therapy was well formulated by Thomas Vicary¹² (1490-1561) when he wrote in 1548 that "in what part of the body the faculty which you would strengthen lies, take the same part of the body of another creature in whom the faculty is strong, as a medicine." Organotherapy has prevailed until recent times, and even today is practiced to certain degrees, although it has become limited to the "glandular pills" and "desiccated polyglandular" nostrums heralded by modern superadvertising campaigns of exploiting patent-medicine makers. Landouzy¹³ in 1898, at a time when the so-called "invigorating" effects of glandular concoctions were blatantly publicized, and when the real functions and actions of the glands of internal secretion were beginning to be scientifically investigated, suggested "opotherapy" as a substitute for the old word "organotherapy" — perhaps to avoid the evil connotation of the latter word, or perhaps because he realized the secretory function and nature of these glands. The name "opotherapy" Landouzy derived from the Greek nouns *οπος*, "juice," and *θεραπεια*, "treatment," but this word never found scientific or popular favor.

Dana¹⁴ in 1916 conferred the title "Author of Opoththerapy and Endocrinology" on Joannes Ursinus,¹⁵ a French physician-poet, who wrote *Protopopoeia animalium aliquot* in 1541. This is an elegiac poem in which Ursinus describes the remedial value and uses of seventy-five animal preparations. Ursinus thus by more than a century preceded Johann Joachim Becher¹⁶ (1635-1682), whose *Parnassus medicinalis illustratus*, written in 1663, dealt with the animal, vegetable and mineral remedies of his time. This remarkable book, written much in the style of the Health Rules of Salerno, both in verse and in prose, contained in four parts more than one thousand pages and twelve hundred illustrations. It mentioned forty animal and twenty-five human substances that supposedly had some remedial value.

Limiting organotherapy to the specific employment of the excretory sex products of the female, either animal or human, which, as is known today, contain certain hormonal ingredients, one finds a

protean assortment of these in ancient and medieval — and even modern — therapeutics. A few of the more repulsive substances and the blatant claims for these remedies will be mentioned.

According to the *Papyrus Ebers*, which is generally dated at about 1550 B.C., the ancient Egyptian pharmacopoeia contained over one hundred groups of preparations, and at least forty of these were animal or human excretions.¹⁷ For instance, the urine of a spouse who had remained faithful to her husband and had known no other man was a remedy for sore eyes. Herodotus¹⁸ (ca. 500–424 B.C.) tells the story of the Egyptian king Phoron, the son of Sesostris, conqueror of Egypt, who had to search diligently for ten years before he could obtain this medicine. He had tried the urine of his wife and of many other women without results. At last he succeeded, married this woman and burned all the others to death — quite a commentary on the morals of those times. Among the ancient Hindus, propagation began with religious ceremonies. Immediately preceding intercourse, an ointment prepared from the dried and powdered penis of a bear and the perirenal fat of a tiger (the kidneys were then regarded as the semen-producing organs) was applied for “prompt action.” Bourke¹⁹ relates many similar tales.

Among the ancient Romans the *Natural History* of Cajs Pliny the Elder²⁰ (23–79 A.D.), who inveterately disliked all physicians, tabulated more than two hundred and fifty remedies of animal or human origin, as compiled by four hundred and seventy-three earlier authors. Pliny²⁰ spoke highly of the medicinal virtues of menstrual blood, not only for the cure of certain diseases but also for killing insect pests at a distance and for quelling storms at sea. Yet it would spoil wine, and dogs licking it would become mad.

In the Middle Ages the Dominican monk Albertus von Bollstädt²¹ (1193–1280), later Bishop of Regensburg, better known as Albertus Magnus, taught at the universities of Paris and Cologne. While lecturing at Paris he recommended powdered testes of hogs in wine for men with poor sexual powers, and powdered uteri of hares, similarly prepared, to render sterile women fertile.²¹ Rondelet²² of Montpellier (1507–1566), is credited by Rolleston²³ with a prescription advocating the dried powder of placenta for the uncomplicated expulsion of the retained secundines after delivery.

Even today such substitution therapy still prevails in the less civilized countries of Europe. The Serbs, for instance, believe that nothing is better for the treatment of impotence than a few dashes of the urine of a pregnant mare, taken in a glass of water.

In this connection should also be mentioned the rejuvenation fad of three decades ago. Rejuvenation in women is even more problematic and uncertain than that in men. The observation of

Steinach and Holzknecht²⁴ that roentgen rays applied to the female pelvis act similarly to vasoligation in males, and that although harming the generative functions of the ovary they produce a proliferation of the ovarian interstitial cells, has not been found true. Zondek²⁵ criticized this theory by stating that Steinach disregarded the fact that during the menopause the follicles are destroyed and that only certain connective tissues remain, holding that not enough interstitial cells that can be stimulated are left. He also attacked as unfounded the suggestion of Liepmann²⁶ that hysterectomy can produce rejuvenation by reason of ligation of the ovarian tubes, and concludes: “On the whole, therefore, the attempts at rejuvenation are hardly adapted to induce an actual renaissance of aged human beings. Such endeavors cannot, indeed, be assumed to harmonize with nature’s plan of organization.”

Although the existence, not necessarily the function, of the testes was known to ancient civilizations because of their external location and easy accessibility, that of the ovary was often not even suspected. Herophilus of Alexandria (ca. 300 B.C.) is credited by Galen²⁷ with the anatomical discovery of the uterine tubes — or *meati spermatici*, as he called them — and with the “female testes,” or *testes muliebris*. He also believed that the male and female semens were transmitted through the “spermatic vessels” and that the tubes passed from the “female testes” to the neck of the bladder, a conception later disproved by Galen.

The Greeks of the Hippocratic era did not know of the existence of the ovaries and thought that the “female semen” was produced as the vaginal secretion during coitus.¹ They believed that conception occurred most easily during the menstrual flow, when girls were conceived, whereas the period immediately after the flow was optimal for the procreation of boys. In this respect their views coincided closely with those of the ancient Hindus. Athenaios of Attalia in Cilicia (ca. 70 A.D.) considered the “female testes” as well as the male breasts as simple symmetrical appendages.¹

Castration of women was already practiced by the ancient Hindus, and Tillmanns relates that even the aboriginal Australian tribes performed operations for artificial hypospadias and ovariectomy to produce impotence and sterility among the unmarried members of their tribes, thus facilitating unproductive sexual intercourse among them.¹

For nearly fifteen hundred years after Herophilus there was little advance in the anatomical knowledge of the female gonads. The discovery of Herophilus was probably lost in the destruction and fire of the great Library of Alexandria by the Arabs in 640 A.D. Galen reigned supreme, although his anatomical concepts were based to a large extent on fancy. So great was the authority of C

Henri de Mondeville (1260-1320) exclaimed with reckless courage "God did not surely exhaust all His wisdom in the creation of Galen."²⁸

The *De Fabrica*, by Vesalius²⁹ (1514-1564), gives an account of the irregular surface of the "female testes," as the ovaries were still called. The name "ovary" originated in 1621 when Fabricius ab Aquapendente³⁰ (1537-1619), who believed that the ovaries contained the "female semen," introduced this name after observing the ovaries of hens. "Ovary" was first applied to human beings in 1667 by Niels Stensen³¹ (1648-1686), who suggested that the vesicles or "blisters" in the female testes were the ova. Also known as Nicolaus Steno, a brilliant student of anatomy, his fame is still associated with the eponym of the excretory duct of the parotid gland and of several other anatomic structures. He is one of the most famous truants of medicine, having at the height of his fruitful scientific career deserted anatomy to find salvation in the Catholic faith and to become titular Bishop of Titopolis. He returned to Copenhagen and remained there for a while as professor of anatomy, and propagated his new faith, but mental conflicts soon forced him to resign again. He died a short time later at the early age of thirty-eight.

Gabriele Fallopio³² (1523-1562), another famous anatomist, successor to Vesalius at the University of Padua, published his *Observationes anatomicae* in 1561. In this book he described in detail the ovaries as well as the uterine tubes, now known by his name, although he did not discover them. He had also observed the corpus luteum, which he described as "velvety vesicles filled with water or a watery fluid sometimes yellow, sometimes like a truly clear swelling." Both Fallopius and Stensen believed that the ovarian follicles were true ova. It was left to the former's pupil Volcherius Coiter³³ (1534-1590) to publicize this observation in 1573, crediting his teacher with it. Coiter himself believed that the ovaries corresponded to the seminal vesicles rather than to the testes and stored the female semen.

The "yellow body" of the ovaries, however, was not described fully or known by this name until Marcello Malpighi³⁴ (1628-1694) studied it carefully with a crude microscope and called it the "corpus luteum" in the appendix (*De ovo incubato*) to the first volume of his *Opera* published in London in 1686. He had found it in virgin as well as in pregnant animals and believed it to be the substance that gave rise to the ovarian follicles, then known as the "ova." De Buffon³⁵ (1708-1788), a Frenchman, however, regarded it as a transient gland that secreted the seminal fluid of the female. It was not until 1766 that Albrecht von Haller³⁶ demonstrated that the corpus luteum was formed by a thickening of the wall of the graafian follicle after its rupture. From this time on the corpus luteum and the follicles were studied in their true physiologic relation.

In 1668 there appeared a book entitled *The Male Generative Organs*, by Regnier de Graaf³⁷ (1641-1673), of Schoonhaven, Holland. In this book is the first account of the nature of the ovarian follicles, then called "ovula." There followed four years later a more detailed study in *De mulierum organis generatione inservientibus*.³⁸ The reasons for the original preliminary note and the subsequent detailed elucidation of the same subject can be found in one of those disputes over priority in which several investigators simultaneously made the identical discovery. There exists a letter of 1668 — unpublished until 1672 — to Werner Rolink (1599-1673) by J. C. van Horne³⁹ in which he described the discovery of the ovarian follicles, then known as ova, prior to de Graaf's first announcement. For details of this chapter in the history of anatomy the reader is referred to the essay of Corner.⁴⁰ De Graaf did not claim priority for his observation. In fact, he spoke of the celebrated van Horne's having made this discovery, but von Haller³⁶ in 1766 coined the eponym "Graafian" vesicle or follicle, because of the detailed study by de Graaf, who rightfully deserves this credit. De Graaf also gave a detailed account of the corpus luteum, describing it as a glandular substance that formed herniations on the "female testes," and foresaw that the ovary formed ova. Rosenmüller⁴¹ in 1802 described originally the epoöphoron, later known eponymically as the "organ of Rosenmüller" or parovarium. The actual human ovum was finally discovered in 1827 by von Baer⁴² after many failures by other investigators.

The general historical background, as well as the development of the nomenclature peculiar to endocrinology, has recently been compiled with special reference to the male hormone.⁴³ A few pertinent notes, however, may be added. The famous physiologist Hufeland⁴⁴ (1762-1836), while a professor at the University of Göttingen, made this interesting statement in 1797: "The organs of generation have the power of secreting the finest and most spiritual parts of our nourishment. But at the same time they are so organized that these perfected and ennobled juices can again return and be received into the blood." Whether this was merely an adaptation of de Bordeu's theory or an original thought is difficult to ascertain. In a fundamental paper King,⁴⁵ of Guy's Hospital, London, in 1836 described the structure and function of the thyroid colloid, and demonstrated its passage into the lymphatics and blood stream as "indirectly surmised by Morgagni." His concept of true endocrine function seems well substantiated in the following excerpt:

Yet we may one day be able to show that a particular material is slowly formed and partially kept in reserve, and that this principle is also supplementary, when poured into the descending cava, to important functions in the course of its circulation, [and] the influence which it exerts upon the circulating fluid may be more or less needful for the healthy subsidence of the entire animal.

In English medical literature the term "endocrine" was first used casually by Crookshank⁴⁶ in February, 1914. In the United States, Halsted,⁴⁷ in one of the Harvey Lectures of the same year, referred to the endocrine glands as "hormonopoeitic." Blair Bell⁴⁸ in 1917 criticized the noun and the adjective "endocrine" and proposed in their stead the words "hormopoeiosis" and "hormopoeitic," respectively, for the ductless glands, a suggestion probably derived from Halsted's lecture. Abderhalden⁴⁹ in 1924 had suggested the word "incretions" for the internal secretions to differentiate them from the "excretions" (waste products), a name originally proposed by Roux in 1919. None of these terms, however, found popular favor, and all soon lapsed into oblivion.

In contradistinction to the singular testicular hormone so far known, the female sex hormones consist of at least two distinct principles: the luteal and the follicular factors, referred to as the progestins and the estrogens. It may be stated that the concept of hormones peculiar to a specific sex, or specific in their action, is no longer valid. Both types of sex hormones occur in either sex in a quantitative relation, and their action depends on the quantitative level and physiologic pathology rather than on specificity. It is preferable, therefore, to speak merely of sex hormones with androgenic or with gynecogenic actions.

At a time when the anatomy of the ovaries and the action or function of their products became known, the general study of endocrine secretions reached the stage of experimental investigation. Yet it is interesting to observe that the hormonal activities of the female gonads were among the last to be suspected, and their principles among the last to be isolated.

Sir Percival Pott⁵⁰ (1713-1788) gave one of the earliest descriptions of the effects of castration of mature women, and the gynecologist Battey⁵¹ (1828-1895), of Rome, Georgia, was among the first to suspect an endocrine function — or rather dysfunction — of the ovaries. In August, 1872, the latter performed the first ovariectomy for physiologic reasons, an event that again led to an acrimonious dispute with English surgeons who claimed priority. Battey had excised the normal and healthy ovaries for the relief of functional disorders, an operation done first only one month earlier at Freiburg, by Hegar. The latter's patient failed to survive, so that Battey deserves the credit for arriving independently at this decision. The rationale of this operation has since been amply justified by the discovery of certain specialized cells in the ovary that have an endocrine function, and the imbalance of which may lead to functional disorders.

Regis⁵² in 1893 claimed that the psychoses of the surgical menopause could be cured by the injection of ovarian juices. His ideas may have been stimulated by the claims of Brown-Séquard⁵³ with testic-

ular extracts. Curâtullo and Tarulli⁵⁴ in 1896 suggested an endocrine function of the entire ovary. Knauer⁵⁵ in the same year observed atrophy of the uterus after removal of the ovaries, but was able to prevent this involution by transplanting ovarian tissues into the castrated animals. Halban⁵⁶ in 1900 demonstrated that ovarian skin grafts brought about normal puberty in guinea pigs castrated in infancy. Adler⁵⁶ in 1912 achieved similar results with crude watery extracts of the ovary when desiccated tissues had failed.

It was at the turn of the last century that Prenant⁵⁷ and Born⁵⁸ independently suggested that the corpus luteum had an endocrine function essential for the maintenance of pregnancy. Clark⁵⁹ in 1900 differentiated between the "true" corpus luteum of pregnancy and the "false" one of menstruation, and Corner⁴ in 1927 finally proved that the corpus luteum is not essential for the occurrence of menstruation. Fraenkel⁵⁸, a pupil of Born, believed the yellow body to be the only source of hormone production in the ovary. Loeb⁶⁰ in 1907 demonstrated specifically that the corpus luteum hormone prepared the uterus for nidation of the fertilized ovum by producing certain progestational changes in the endometrium, irrespective of whether pregnancy follows. If pregnancy did not take place, its effects resulted in a desquamation of the uterine mucosa — that is, in menstruation. Finally, Fraenkel⁶¹ in 1910 proved the endocrine function of the corpus luteum.

Long before anything was known about the corpus-luteum hormone, physicians differentiated "desiccated whole ovary" and "desiccated corpus luteum" preparations. It was then not realized, however, that neither had any therapeutic effects, since the concentration of hormones in them was negligible. It is claimed that virtually tons of desiccated ovarian tissue would be necessary to produce even minor estrogenic effects, and that no effective amounts of corpus-luteum hormone could ever be administered by such "ovarian pills." Frank⁶² stated in 1931 that "such things as desiccated ovary, desiccated testes, thymus and anterior-pituitary extracts can be given by pound or bushel, and the only effect that I can notice is a disturbance of a delicate stomach."

The qualitative as well as the quantitative determination of the luteal hormone — or of any hormone — depends entirely on reliable methods of detection and assay. The ideal methods are those of chemical reactions, but these, as in so many other endocrine products, are not yet feasible. Recourse has therefore to be taken to biologic methods. For this purpose there are available two methods for the assay of the luteal principle. The first, discovered by Corner and Allen⁶³ in 1929, utilizes a sexually mature rabbit, since its ovaries always contain ripe follicles, and since its uterine mucosa is always in the proliferative stage. An injection of

luteal extracts or of pure hormone transforms this mucosa into a "pregnant" or "pseudopregnant" state.

The second method was developed by Clauberg⁶⁴ in 1930, and consists of bringing the infantile uterine mucosa of an immature rabbit into the proliferative stage by preliminary injections of follicular hormone. This is usually achieved after eight daily injections of ten mouse units. The luteal hormone to be assayed is then injected until a pseudopregnant uterine mucosa develops. The smallest amount of luteal hormone that will produce this result is the unit of potency, or rabbit unit. The standard, or international, unit was determined at the International Conference for Biological Standardization in London in 1935.⁶⁵ It is the equivalent of 1 mg. of the crystalline corpus-luteum hormone (beta progesterone) preserved in London.

Practicing physicians waited anxiously for a pure corpus-luteum extract, since many uses and indications had been theoretically foreseen. Hannes⁶⁶ in 1919 attempted to prevent spontaneous abortion with crude extracts. The mechanism of premenstrual tension was postulated by Frank⁶² in 1931, and Novak and Reynolds⁶⁷ in 1932 defined the motility factors underlying functional dysmenorrhea. Engle and his co-workers⁶⁸ after a series of careful studies suggested the importance of the luteal principle in the functional uterine bleeding disorders.

Weichert⁶⁹ in 1928 demonstrated the action of the corpus luteum hormone by the observation of definite changes in the uterus of animals, as previously described by Loeb⁶⁰ in 1907. For his experiments he used crude corpus-luteum extracts and injected them into the test animals. His claims were soon confirmed by other investigators. Corner and Allen⁶³ in 1929 prepared the first crude extract of luteal hormone from the ovaries of swine. Allen and Wintersteiner⁷⁰ and Butenandt and his co-workers⁷¹ in 1934 succeeded in isolating a crystalline form of the hormone. They determined its structure as a di-keto-steroid, with the empirical formula $C_{21}H_{30}O_2$. The final achievement, however, was the synthetic production of this hormone in pure form by Butenandt's⁷² laboratory, and soon by others, who prepared it from the stigmasterol portion of soy beans. This synthesis made possible extensive clinical study and application, since the hormone was completely reliable and free from other related compounds and side effects.

It is interesting to note that the natural hormone occurs in an extremely small relative quantity, in a ratio variously estimated as 1:40,000 in the human corpus luteum and 1:750,000 in the human placenta. The pure principle is now also synthesized from pregnanediol,⁷³ a progestin and excretion product found in pregnancy urine. The clinical results obtained with the pure hormone have substantiated the theoretical predictions, but even today its

effects have not been explored in their entirety. Clinical results depend on a chemically pure hormone of exactly known potency and of complete reliability.

The early terminology of the corpus-luteum hormone was variegated and confusing, because of the numerous nonproprietary and proprietary names for the same substance. Corner and Allen⁶³ called it "progestin" on account of its progestational activity. Hisaw preferred the name "relaxin"⁷⁴ for one principle because of its ability to relax the sacral and pubic ligaments in pregnant rodents, and the name "corporin"⁷⁵ for a similar factor because of its origin in the corpus luteum. Clauberg⁶⁴ used the names "lutein" and "proluton" for similar reasons, and Slotta⁷⁶ coined the terms "luteo-steron C and D" because of the steroid nature of the compounds. Finally, to prevent further confusion the leading investigators from all countries met in 1935 and agreed to use henceforth only the term "progesterone,"⁷⁷ which proved acceptable to all and is now the nonproprietary designation for the luteal principle. It is, however, limited to the pure crystalline hormone, the term "progestin" being used to denote the whole group of progesterone-like, or impure, substances.

Chemically, progesterone, as isolated in 1934, is pregnenedion-3-1-20-ol, and has the empirical formula $C_{21}H_{30}O_2$. It exists in two isomeric forms in the solid state only, and either of these forms can be easily converted into the other. In solution both forms are chemically and physiologically identical. Progesterone is synthesized from the stigmasterol portion of soy beans and from the pregnanediol of pregnancy urine. The orally effective derivative pregneninolone was discovered by Inhoffen and Hohlweg⁷⁸ in 1938 by the addition of an ethinyl radical to the follicular or the androgenic principles.

Although the corpus-luteum principle was at first the only female hormone suspected and sought, the early investigators soon realized that there must be at least another factor — and source of hormones — in the ovary. Marshall⁷⁹ in 1905 suggested that either the interstitial or the follicular cells of the ovary also secreted a hormone that would produce estrus. Halban⁸⁰ in the same year found that this follicular factor stimulated growth of and produced changes in the breasts. Adler⁵⁶ in 1912 produced estrous changes by the injection of watery extracts of the ovaries into virgin animals. Iscovesco,⁸¹ and independently Fellner,⁸² and several others in the same year prepared certain lipid extracts of the ovary that produced hyperemia in the uterus of castrate and immature rodents.

The name "estrus" is the same as the Latin word for gadfly, and was used figuratively to indicate intense sexual frenzy or heat in animals. It designates the restricted period of mating activity of female mammals, but not that of the primates. Recent experiments with the ovarian hormones have em-

phasized another aspect of estrus — namely, the rapid growth of the accessory sex organs. This growth introduces the period of rut proper, and is brought about by the follicular hormone. The follicular hormone is therefore primarily a growth hormone, whereas the luteal hormone does not have this property.

The earliest test for the follicular factor was developed by Aschner⁸² in 1913. He had observed in castrated female rodents growth of breasts and nipples and hyperemia of the vagina and the uterus three to seven days after the injection of ovarian and placental extracts. When Stockard and Papanicolaou⁸⁴ in 1917 discovered a typical estrus cycle in the guinea pig the phases of which could be accurately determined by the presence of certain cornified epithelial cell changes in the vaginal smears with beginning rut, an important forward step was made. This phenomenon was utilized by Allen and Doisy⁸⁵ in 1923 to develop a method for studying qualitatively the actions of this hormone. They observed changes from the normal leukocytes of the vagina of castrated rodents to cornified epithelial cells and squamous scales two or three days after the injection of follicular extracts, changes that occurred normally only in estrous females. Simultaneously they announced for the first time the isolation of a comparatively pure crystalline substance obtained from the follicular fluid of cows and sows, 3 mg. of which induced estrus in a rat; this amount they called "1 rat unit."

Less popular tests were developed in 1925 by Frank,⁸⁶ who claimed that the delay in contractions of the uterine strip when suspended in Ringer's solution was in proportion to the concentration of preceding hormone saturation. Blotvogel⁸⁷ noted an increase of the chrome-staining cells of the pericervical lymph nodes of castrated animals after injection of active follicular substances.

With such growth-indicators as measures of qualitative and quantitative biologic changes, the other sources of estrogens could be found and assayed in animal organs as well as in plants, and even among minerals. The collective term "estrogenic principle" refers to any substance that induces the growth of the accessory sex organs.

Courrier⁸⁸ in 1924 studied the action of this hormone on the menstrual cycle, and because of its importance in producing the follicular phase called it "folliculin," a name still commonly used. A year later Laqueur⁸⁹ coined the term "menformon," now used as a proprietary name. Glimm and Wadehn⁹⁰ preferred the word "feminin" for this principle. In 1925, Loene⁹¹ demonstrated the occurrence of follicular substances in the urine and the blood of normal women and called it "thelykinin" to signify its feminine activity. Collip⁹² named it "emmenin" after obtaining it from the placenta. It is to the credit of Parkes and Bellerby⁹³ to have introduced the term "oestrin" in 1926, a name later modified to

"estrone," designating the nonproprietary form for the follicular hormone.

Estrone is a fat-soluble principle derived from sterols. It was extracted in 1927 by Doisy,⁸⁴ who named it "theelin." Butenandt⁹⁴ in 1929 independently isolated and crystallized it, with the empirical formula $C_{18}H_{22}O_2$, and called it "progynon," a term also retained as a proprietary designation. Marrian⁹⁵ in 1930 isolated the excretory form of this hormone, known then as "theolol." It soon became evident that this hormone existed in numerous chemical forms with varying degrees of physiologic action.

The basic structure of the follicular principle is estratriene $C_{18}H_{22}$, empirically identical with estrane, the basis of all sex hormones, female as well as male. Estrone, or 17-keto-3-hydroxy estratriene, was synthesized by Butenandt⁹⁷ in 1933 from palm nuts, but is not the true secretion of the follicular cells. The actual hormone is estradiol, which was obtained in pure form by Schwenk and Hildebrandt⁹⁸ in 1933 by the reduction of the keto-form to an alcohol, and what has the empirical formula $C_{18}H_{24}O_2$.

To eliminate the confusion of different names and different potencies, the Health Organization of the League of Nations⁹⁹ in session at London in 1931 designated as the international unit 0.1 gamma of the pure crystalline substance estrone, since the true principle estradiol was not yet isolated. This unit is about one third as active as the original Allen-Doisy rat unit, and is based entirely on gravimetric measures. It makes no reference to the estrous effects in castrated rodents. In order to prevent misinterpretation with later preparations a second international standard was adopted in 1935 for the less potent but longer-acting benzoylated derivatives,⁶⁵ as measured by the benzoic acid ester of alpha estradiol, the di-hydro-estratriene, but even then its estrogenic equivalent to the keto-hydroxy form estrone was not defined.

The bursting human follicle contains 2 or 3 cc. of follicular fluid with an estrogenic equivalent of 8 to 12 mouse units.²⁵ Zondek and Aschheim¹⁰⁰ in 1927 demonstrated that the hormone is most likely produced by the thecal and granulosa cells of the follicle, but Allen¹⁰¹ believes that all ovarian tissues may produce it, as well as the corpus luteum and the placenta. It is not peculiar to the female, for Haussler¹⁰² in 1934 found that the urine of stallions contains five hundred times higher titers of it than do those occurring in the ovaries of mature mares.

It is not within the scope of this essay to discuss the chemical and physiologic interrelations of the sex hormones or their clinical status, all of which command an enormous literature. Brief mention, however, should be made of the nonbiologic estrogens used clinically. There are at least forty known substances with estrogenic activity, and among these the only nonbiologic compound so far

used belongs to the stilbestrol group. Cook and Dodds¹⁰³ studied hydrocarbons intensively and found that many had estrogenic activities. Schwerdtfeger¹⁰⁴ in 1931 demonstrated that some sea animals and insects possess estrogenic substances, whereas Silberstein and his co-workers¹⁰⁵ found them in actively growing bacterial cultures. Finally, Dodds¹⁰⁶ in 1938 discovered the stilbene compounds, which were unusually active in minute doses, and called the basic substance 4, 4-dihydroxystilbene "stilbestrol." The most promising of its derivatives is now known by the nonproprietary name "diethylstilbestrol," or 4, 4-dihydroxy- α - β -diethylstilbene. Clinically it acts like the natural estrogens but has some unpleasant side effects. It is not a steroid and is easily and cheaply prepared from common chemical reagents.

* * *

Thus ends the story of one of the most fascinating chapters of medical history. Primitive man, limited by the faulty observations of inexperience, cannot be condemned for imitating Nature in eating indiscriminately certain excretory substances in the hope of saving his life. One must marvel at the way in which progressive minds at the risk of death as heretics tried to advance human welfare but failed because of deficient knowledge, jealously guarded by despotic authority. Yet the pendulum swung on through the depth of the dark centuries, to reach its climax in the speculative theories of a century of enlightenment. But even logic failed because it was based on erroneous premises. Finally the pendulum swung back through another century that witnessed the beginning of exact experimental science, and completed its course only a few years ago when the chemical nature of the hormones was discovered.

The speculative mind does not rest, but wonders at the ingenuity of the chemical laboratory of the human body, not yet duplicated by creative powers. Whither will it lead? The close relations of vitamins, hormones and carcinogens are known. Will the human mind finally conquer in spite of the obstacle still deemed unsurmountable? But guessing is futile — unless based on facts and proved by experiment.

So one can do no better than epitomize the past in chronological order and await the revelations of the future:

- 1550 B.C. The *Papyrus Ebers*, the oldest medical book known, mentions more than forty animal and human products as remedies.
- 1400 The *Ayurveda* by Susruta regards menstruation as a periodic cleansing of the body, and mentions several organotherapeutic remedies for sexual disorders.
- 460 Hippocrates of Cos describes 2 cases of menopausal hirsutism. Greek medical ethics recognizes the sanctity of motherhood.
- 300 The Greeks know the testes but not the ovaries. Herophilus of Alexandria discovers the "female testes" or ovaries and the *meati spermatici* or ovarian tubes.

- 70 A.D. Pliny the Elder mentions the remedial qualities of menstrual blood among more than two hundred and fifty medicines of animal or human origin, as compiled by four hundred and seventy-three authors.
- 1250 Albertus Magnus recommends powdered uteri of hares as a remedy for female sterility.
- 1300 Henri de Mondeville assails the supremacy of Galen.
- 1541 Jean Ursinus, a French physician-poet, was subsequently called by Dana "the Author of Opothrapy and Endocrinology."
- 1548 Thomas Vicary states the rationale of organotherapy.
- 1555 Andreas Vesalius describes the "irregularities" of the "female testes."
- 1561 Gabriele Fallopio describes the ovarian tubes and the yellow body of the ovary.
- 1575 Guillaume Rondelet advocates dried placenta for uncomplicated expulsion of retained secundines.
- 1621 Fabricius ab Aquapendente describes the ovaries of hens.
- 1663 Johann Joachim Becher's *Parnassus medicinalis illustratus* mentions forty animal and twenty-five human substances as remedies.
- 1667 Niels Stensen uses the name "ovary" for "female testes."
- 1668 J. C. van Horne discovers the ovarian follicles, but Regnier de Graaf describes them in detail.
- 1691 François Mauriceau suggests that conception is independent of menstruation.
- 1686 Marcello Malpighi coins the name "corpus luteum."
- 1690 Heidentrijk Overkamp believes that the "ova" — that is, follicles — secrete a substance into the circulating blood.
- 1696 Nicholas Venette believe that this substance causes menstruation.
- 1756 Percival Pott describes the effects of removal of the healthy ovaries in a young woman.
- 1766 Albrecht von Haller coins the eponym "graafian follicle."
- 1776 G. L. D. de Buffon regards the corpus luteum as the gland that secretes the "female semen."
- 1802 J. C. Rosenmüller describes the epoöphoron since known by his name.
- 1827 C. E. von Baer discovers the human and mammalian ova.
- 1872 Robert Battey for the first time intentionally removes the ovaries for menstrual disorders, an operation since known by his name.
- 1896 Curatello and Tarulli suggest an endocrine function of the ovary.
- 1898 G. Born and independently A. Prenant suggest an endocrine function of the corpus luteum.
- 1905 F. H. A. Marshall mentions a follicular hormone.
- 1910 L. Fraenkel proves the endocrine function of the corpus luteum.
- 1913 B. Aschner devises the first biologic test for the follicular hormone.
- 1919 W. Hannes for the first time uses corpus luteum extracts to prevent spontaneous abortion.
- 1923 E. Allen and E. A. Doisy devise the best test for, and isolate, the follicular hormone.
- 1929 G. W. Corner and W. M. Allen discover a biologic test for, and prepare the first crude extracts of, corpus-luteum hormone.
- A. Butenandt and independently E. A. Doisy crystallize the follicular hormone estrone.
- 1933 A. Butenandt synthesizes the follicular hormone from palm-nut oil.
- E. Schwenk and F. Hildebrandt obtain the true follicular hormone estradiol by reduction of estrone.
- 1934 A. Butenandt and independently W. M. Allen and O. Wintersteiner crystallize the corpus-luteum hormone progesterone.
- A. Butenandt synthesizes progesterone from soy beans.

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SWEAT AS A CULTURE MEDIUM FOR FUNGI*

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IT HAS been realized that sweat can support the growth of fungi and that its excessive secretion is often the determining factor in infection. It is common to observe the presence of hyperhidrosis with eczematoid ringworm of the hands and feet. One of

by clinical observations, depends on an unconcentrated medium. The same material after concentration by evaporation has antiseptic powers. Peck, Rosenfeld, Leifer and Bierman² have shown that thermal sweat may have fungistatic properties acid

TABLE 1. Description of Plate Cultures.

TYPE OF EXAMINATION	SWEAT AGAR	SABOURAUD'S MEDIUM
<i>Trichophyton purpureum</i>		
Macroscopic	The colony had the same character as when the mold was grown on Sabouraud's medium except that it was smaller and growth was not so luxuriant.	The colony produced was thick and white, with a central umbo, and had a velvety appearance. The back of the colony displayed a typical rose-purple color. A minimum of aerial growth was present.
Microscopic	Mounts prepared from a giant colony 1 month old showed many microconidia, a few fuseaux and a racquet mycelium.	Mounts prepared from colonies showed numerous microconidia and a racquet mycelium. A fairly large number of fuseaux were seen.
<i>Trichophyton gypsum</i>		
Macroscopic	The colony had the same character as when the mold was grown on Sabouraud's medium, but it was smaller and growth was not so luxuriant. Two concentric zones were clearly apparent.	The colony produced was white and fluffy and had a boss at the center. It showed many aerial mycelia.
Microscopic	Mounts prepared from a giant colony 1 month old showed microconidia, a branched, segmented mycelium and a few spirals. No fuseaux were seen.	The mycelium was septate. Numerous microconidia, a racquet mycelia and several blunt end fuseaux were seen.
<i>Microsporum gypsum</i>		
Macroscopic	The colony grew more rapidly than those of other species but was a scant filamentous growth and attained a greater diameter than did the other colonies.	The colony showed a white, felty growth with a large central umbo. Later it assumed a yellowish color.
Microscopic	Mounts prepared from a giant colony 1 month old showed a racquet mycelium, numerous microconidia and an occasional fuseau.	Mounts showed a racquet mycelium. Numerous microconidia and fuseaux were present.
<i>Hormodendrum</i> species		
Macroscopic	Growth was very slow. A flat rather smooth colony with a fringe of aerial mycelium around the edge developed.	The colony was dark olive-green with a grayish nap. It presented zones, but they are not apparent in the photograph.
Microscopic	Mounts prepared from a giant colony, 1 month old, showed yeastlike spores in groups along the side of a segmented mycelium and also at the tip.	Numerous dark-brownish, yeastlike spores appeared in groups along the mycelia and at the tips.

us (T.C.¹) has shown experimentally that such infection can be clinically induced by conditions that favor increased sweating of the feet.

The growth of fungi in sweat, as demonstrated in the experiments reported in the present paper and

in reaction (below pH 7.0), particularly when concentrated, and that these properties depend on its content of acetic, proprionic, caproic, caprylic, lactic and ascorbic acids. They have also found topical applications of these acid ingredients of sweat to be valuable in the treatment of fungus infections.

Bergeim and Cornbleet³ believe that freshly secreted sweat may have a mild antiseptic action,

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owing largely to its acid reaction, for which lactic acid is mainly responsible. Evaporation of such sweat on the surface of the skin or elsewhere tends to lower the pH and to increase the concentration of lactic acid so that the sweat becomes much more effective in this regard.

Tests on incubation of sweat show, however, that there is also a tendency for the sweat to become alkalized owing to formation of ammonia by bacteria from the urea present. On the other hand, ammonia is more volatile than lactic acid, so that on evaporation much of it is lost and much of the lactic

In the present experiments, sweat was obtained by encasing the subjects as far as their necks in a rubber bag while they were seated in a heat cabinet. Incandescent lamps furnished sufficient heat to obtain from 100 to 200 cc. of sweat in twenty to thirty minutes. Collected material was passed through a Berkefeld or Seitz filter, and control samples of filtered sweat were observed for sterility. Tubes of freshly filtered sweat were inoculated with the fungi. A solid medium was also prepared and used in Petri dishes in the usual manner. This medium was made by autoclaving a 4 per cent solution

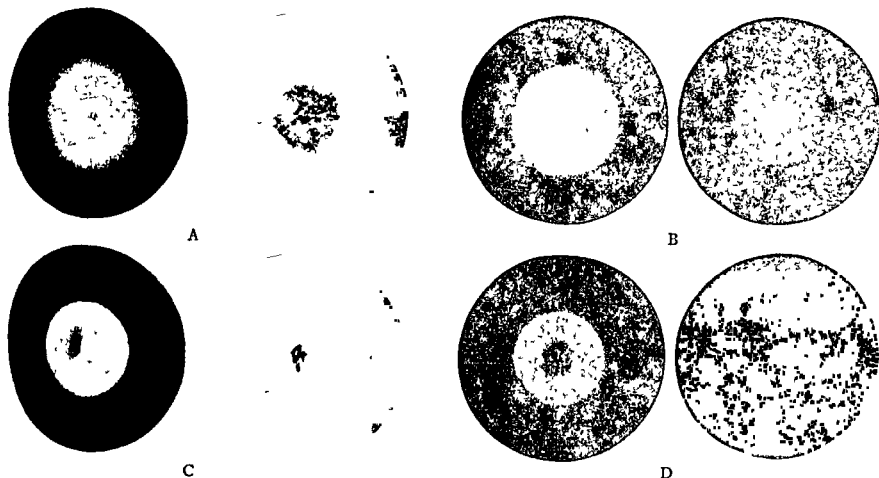


FIGURE 1. One-Month-Old Cultures on Sweat Agar.

The cultures on the left are on Sabouraud's medium, and those on the right are sweat agar. A — *Trichophyton purpureum*; B — *Trichophyton gypsum*; C — *Microsporon gypsum*; D — *Hormodendrum species*.

acid is regained. The volatile fatty acids are largely if not entirely formed on the surface of the skin by bacterial action on the lactic acid. Above pH 5.3 lactic acid is so completely ionized that few undissociated molecules of acid — on which much of the antibacterial action of the acid must depend — are present. The chief protective value of this acid lies, therefore, below pH 5.3. The volatile acids are less dissociated, and hence more effective, in the pH range of 5.3 to 6.2. Their most important role thus appears to be the extension of some degree of acid protection into these higher pH levels, which under certain conditions exist also on the skin.

Sweat is therefore capable of having quite diverse actions toward fungi, depending largely on the degree of evaporation that takes place. This parallels events in a solution of sugar; the diluted material can be attacked by fungi, whereas the concentrated material cannot. The changes in acidity or alkalinity are of course also important in determining the action of sweat on the fungi.

of agar at 15 pounds' pressure for twenty minutes. Four cubic centimeters of autoclaved agar solution was added to 6 cc. of sterile sweat, which had previously been heated to 50° C., and the mixture was poured into a sterile Petri dish. The material solidified and appeared like other agar media. The tubes of sweat and Petri-dish preparations were inoculated with fungi — *Trichophyton purpureum*, *Trich. gypsum*, *Microsporon gypsum* and *Hormodendrum species* — obtained from patients with cutaneous infections.

Transfers from the first cultures prepared in sweat were made to sweat-agar Petri dishes in order to obtain giant colonies. It was necessary to make transfers approximately three times to fresh dishes during the course of the work, because contaminants had entered the original dishes during the long incubation period and the latter were therefore unsuitable for the taking of photographs. Colony growth was the same each time, and no pleomorphism was observed. One-month-old cultures were used in all

cases for the photographs (Fig. 1) and descriptions (Table 1).

For the tube cultures, transfers were made of each fungus to tubes of sweat that had been previously filtered through a Seitz filter and allowed to incubate at room temperature. Growth was slow in starting but grew well after the initial lag. Consid-

these tubes after an incubation period of one month. The cultural characteristics are given in Table 2.

DISCUSSION

The superficial fungus infections of the skin take place within or on the keratin layer. It is well known



FIGURE 2. One-Month-Old Cultures in Sweat.

Starting at the left, the cultures are, respectively, as follows: *Hormodendrum species*, *Microsporon gypseum*; *Trichophyton purpureum*; and *Trich gypseum*.

erable evaporation had taken place after one month, so subcultures were made to a second series of sweat

TABLE 2 Description of Tube Cultures.

<i>Trichophyton purpureum</i>	The fungus grew slowly and was white and velvety on the surface of the liquid. There was also a small amount of growth at the bottom of the tube.
<i>Trichophyton gypseum</i>	The fungus grew slowly and was white and velvety on the surface of the liquid. No growth took place at the bottom of the tube.
<i>Microsporum gypseum</i>	The fungus grew rapidly, producing a white, felty mycelial growth about 1 cm. in height on the surface. There was a small amount of growth at the bottom of the tube.
<i>Hormodendrum species</i>	The fungus grew very slowly, and there was more growth at the bottom of the tube than at the top. Mycelial growth was below the surface, while the surface growth was smooth and leathery.

tubes. These subcultures grew more rapidly than the initial ones did. The photograph (Fig. 2) shows

that keratin and related products serve well for the growth of fungi; thus, they are found growing on feathers and leather. Keratin is rich in sulfur-containing amino acids, and this raises the question of the relation of this element to fungus growth. If the sulfur is a requirement for the thriving of fungi, it must be present in such a form as not to lead to the production of sulfides. Cornbleet and Bergeim⁴ have found that fungi are extremely sensitive to hydrogen sulfide and are killed or prevented from growing by extremely small concentrations.

Fungi also need moisture for growth and this is furnished by the sweat, but sweat alone can support

the growth of fungi, as shown in the above observations. Just what factor in sweat is the chief support of growth cannot be said. There are lactic acid and also volatile fatty acids. Some observers⁵ have found sugar in sweat, although this conclusion may have resulted from the presence of reducing substances. There are sulfur-containing substances, although cultures of the hyphomycetes in sweat that were tested did not contain hydrogen sulfide. The same mediums, however, used for growing a number of varieties of bacteria did contain it.

So far as can be seen at the present, this study cannot be put to practical use. It may be that sweat mediums will be found to be useful for the differentiation of certain species that is difficult by other means. Such capacity was not shown in this study, but only a few varieties of fungi were used. No pleomorphism was shown for any of the cultures in three months of observation, so that they are fairly stable on these mediums.

SUMMARY

A description is given of several fungi that were grown on sweat and a medium made of sweat and agar.

The role of sweat as an antiseptic and as a nutritive source is briefly reviewed.

Certain aspects of the natural growth of the hyphomycetes on the skin are considered, and the relation of some constituents in sweat to this growth are discussed.

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MEDICAL PROGRESS

GYNECOLOGY: CARCINOMA OF THE CERVIX (Concluded)

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THE series of cases reported in Table I have been classified by the League of Nations method and are from clinics large enough to have a sufficient number of cases to be significant. These results have been accepted by the Health Organization of the League of Nations and have been analyzed by Heyman.²⁰ They show how little variation there is from class to class and from total to total. There is no single way to treat cervical cancer, and Miller's² remarks, quoted at the beginning of this paper, cannot be better proved than by these results. It will be seen that the widest variation is in the Class III cases, and here is the greatest chance for errors in diagnosis, for some of these patients may have had only inflammatory nodes or masses and not cancerous masses, and thus an advanced case may have been reported as cured. If one could eliminate the Class III cases, there would be a close consistency of results. This discrepancy is probably due to incorrect evaluation, possibly to a better method of treatment.

In the surgical cases, Bonney's²⁷ curability of 40 per cent of those operated on is the only figure of consequence available.

PROGNOSIS

A prognosis cannot be made from a study of microscopic slides alone. Since slowly growing tumors may be radioresistant and since rapidly growing

tumors may respond but metastasize rapidly, it is the cases with a moderate grade of malignancy that do best. Early cases do better than late ones. Cases with distant metastases have a high mortality. If a patient has symptoms for more than six months, she is usually in the inoperative and incurable group. Goldscheider³⁴ believes that pyrexia in the course of x-ray treatment is an unfavorable sign. In order to evaluate the results of a method of treatment in a shorter time than five years, Meigs and Jaffe³⁵ were able to show that if 10 per cent is deducted from the three-year survivals for the fourth year and 5 per cent for the fifth year, the five-year end results can be estimated. Warren, Meigs, Severance and Jaffe³⁶ showed in a study of biopsy material taken before, during and after combined radium and x-ray treatment that if a tumor does not respond to treatment, as shown by destruction of cells, abnormal mitoses and an increase in connective tissue, the outlook is usually fatal. Nilsson³⁷ believes that the prognosis in cases of adenocarcinoma of the cervix is not so favorable as that in squamous-cell cancer, but his findings are not borne out by other authors.

COMPLICATIONS

The complications of cervical cancer that are due to its growth alone are destruction of the bladder and rectum and blockage of the ureters. Later in the progress of the disease hemorrhage and distant metastases to vital organs occur.

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Vesicovaginal fistula and rectovaginal fistula in untreated cervical cancer are not rare. Smith³⁸ believes that fistulas are twice as frequent in untreated cases as in treated ones and that they are evidence of advanced disease. He estimates the incidence of rectovaginal fistula as in 75 cases, that of vesicovaginal fistula as 1 in 92 cases and a combination of both as 1 in 129 cases. Death in untreated cases is often due to ureteral block and uremia. If it is desired to stop severe hemorrhage from a cervical cancer because of the favorable aspect of the

cases with serious bowel injury, comprising about 2 per cent of the total number of cases treated. This injury is probably a small price to pay in the treatment of this disease, but it may indicate that too heavy treatment with the x-ray machine is being used. It is also true, however, that the same injury may occur with radium alone. Wigby⁴⁴ in 1943 reported some reaction in the sigmoid in 24 out of 100 patients. The injuries included hyperemia and edema, ulceration and bleeding, edema and pain, and obstruction. Pyometrium, peritonitis, pelvic

TABLE 1. Analysis of Results of Treatment for Carcinoma of the Cervix.

INSTITUTION	STAGE I		STAGE II		STAGE III		STAGE IV		ALL STAGES	
	NO. OF CASES	PERCENT. CURED	NO. OF CASES	PERCENT. CURED	NO. OF CASES	PERCENT. CURED	NO. OF CASES	PERCENT. CURED	NO. OF CASES	PERCENT. CURED
Memorial Hospital (New York City)	17	52.9	15	46.7	74	18.9	30	10.0	136	24.3
Woman's Hospital (New York City)	9	55.5	24	25.0	18	16.7			51	27.3
University of Brussels (Brussels)	6	33.3	20	40.0	28	14.3	9	0.0	63	22.2
Liverpool Radium Institute (Liverpool) .	8	62.5	28	25.0	43	14.0	15	0.0	94	19.1
Marie Curie Institute (Paris)	9	66.6	20	60.0	75	30.7	22	4.5	126	33.3
Radium Center (London)	4	25.0	27	11.1	37	18.9	19	0.0	87	12.6
Institut du Cancer (Paris)	9	44.4	15	53.3	40	35.0	19	10.5	83	33.7
Institut du Radium (Paris)	12	66.6	44	43.2	34	32.3	12	8.3	102	38.2
Radium hemmet (Stockholm)	31	48.4	67	26.9	71	8.5	42	9.5	221	20.4
All reporting hospitals	607	55.2	1626	36.3	2417	21.2	1020	5.3	5672	26.3

growth, Leventhal, Lash and Grossman³⁹ advise extraperitoneal ligation of the hypogastric arteries. This should not be difficult to accomplish.

Ureteral block is not uncommon. Graves, Kickham and Nathanson⁴⁰ reported from the Pondville Hospital that 70 per cent of their cases had obstruction of the ureters and that complete urologic investigation was necessary. Also reporting from this hospital, Jaffe, Meigs, Graves and Kickham⁴¹ state their belief that management of the obstructed ureters by means of nephrostomy frequently saves the kidneys. Treatment is omitted while the temperature is high and is resumed after nephrostomy has allowed it to return to normal. After the edema has subsided and cancer has been destroyed, the ureter may function normally. It was due to the above investigations at the Pondville Hospital that the Urologic Clinic dealing with the urologic complications of cervical cancer was established there.

Bowel injury following radiation treatment is not infrequent. Jones,⁴² and later Aldridge,⁴³ have reported a series of serious injuries to the bowel by x-ray treatment. Jones describes severe injuries in 7 of 520 treated cases. In 5 of these the large intestine was affected, and in 2 the small intestine. Aldridge thinks that in many cases sufficient radiation to cure the patient cannot be given without damage to the intestinal tract. A great many of the manifestations of bowel injury, such as diarrhea, tenesmus and bleeding, are simple, but at a subsequent time—from months to years later—cicatriziation may occur, with damage to the small or large intestine, necessitating colostomy to allow the bowel to heal or hemorrhage to cease, or even resection of the small or large bowel for obstruction. From the clinics at the Massachusetts General Hospital and Pondville Hospital I have collected 47

inflammation and so forth may follow combined radium and x-ray treatment. Philipp⁴⁵ and later Miller and Folsome⁴⁶ have reported fractures of the neck of the femur following radiation treatment for cervical cancer. This has led to the elimination of the lateral portal for treatment in some clinics. Martin⁴⁷ recognizes the danger of radiation and has tried to prevent untoward reactions. He has substituted multiple sources of radium of moderate intensity and frequently shifts containers of high intensity. He increases the distance for vaginal applicators by means of vaginal packs. He changes the packs frequently, uses no radon implants, avoids the ureters and employs intensive x-ray treatment only in advanced cases. He has elevated the lateral portals of treatment and gives his therapy in one careful series. He also allows a long interval between x-ray treatment and radium treatment. With all these measures I cannot agree, but the steps Martin is taking show that he has encountered difficulties, as have all clinics, and is searching for a way out of them.

CAUSES OF DEATH

The cause of death in most patients with cancer of the cervix is interference with the urinary tract, blocking of the ureters and uremia. Hemorrhage is a not infrequent complication, and large fatal ones due to erosion of a large artery are not uncommon. Many patients with cancer of all kinds die of persistent depletion due to loss of weight, lack of appetite, obstruction of the bowels, pyrexia and so forth.

PREVENTION

Improvement in the methods of reconstruction of cervical injuries comprises one means for the prevention of cervical cancer. The use of office cautery

and repair or operation on the cervix will surely aid in avoiding cancer, but even perfect repair or perfect reconstruction will not prevent it if all the cancer-producing factors are present. It is not known how long it takes malignant disease to develop, how it starts or from what sort of tissue it arises.

The best method of prevention is excision, and the only type of excision that completely removes the cervix is total hysterectomy. This cannot always be advocated, but with the decreasing mortality from this operation it is probable that the number of unsuspected cervical cancers found in the laboratory will approximate the number of deaths from the operation. No one can advocate removal of the uterus and cervix in every married woman over the age of thirty, but one can properly advise, if for any reason abdominal operation is necessary, not that repair, cauterization and amputation be done but that the uterus and cervix be completely removed. This can be called radical advice, but to one who has seen cervical cancer develop in 2 cases after cauterization and supravaginal hysterectomy it does not seem at all radical. If total hysterectomy cannot be done with so low a mortality as supravaginal hysterectomy, each case should be sent to someone who can do it. A discussion of cancer of the cervical stump will be given later.

Schmitz,⁴⁸ Macfarlane et al.⁴⁹ and Phaneuf and Belson⁵⁰ advise observation of the cervix. Schmitz says that this should be made once a year; Macfarlane, who examined 1000 women, says twice a year; and Phaneuf and Belson biopsied 100 consecutive patients. Macfarlane et al. found 4 cases, and Phaneuf and Belson also found 4 cases. The early recognition of cancer is so difficult that in any suspicious case it is much safer to remove the cervix than to leave it, and total hysterectomy is the best method of prevention.

Von Graff⁵¹ found that cancer of the body of the uterus was nine times as frequent and cancer of the cervix four times as frequent in patients with fibroids as in those with a normal uterus, so that in such cases total hysterectomy is the procedure of choice.

PREMALIGNANT LESIONS AND VERY EARLY CANCER

The question of premalignant lesions is a much disputed one, and it is not yet clear what part epidermalization and squamous-cell metaplasia play in the development of cancer of the cervix. Knight⁵² in reporting 17 cases of superficial epithelioma states that cancer occurs not infrequently in tissue that has undergone squamous-cell metaplasia. He believes that the latter may be important and may be the early phase of intraepithelial cancer. Mezer⁵³ in a careful study of 1636 cases of polyp found 5 with cancer; in all of them the polyps were associated with squamous-cell metaplasia. It is doubtful that the time has yet come when total hysterectomy can be advocated by the pathologist because of the

finding of epidermalization and squamous-cell metaplasia, for such conditions have been seen in patients who have been followed for many years after the diagnosis was made. Nevertheless, it is also obvious that such a condition cannot be overlooked and that a careful follow-up for years is essential.

The question of cancer in situ, or intraepithelial or preinvasive cancer, is also not yet decided, but it is recognized by such an authority as Meyer⁵⁴ as being carcinoma. The experience of many is that if cancer in situ is present in a biopsy specimen, there may be invasive cancer in some other area in the cervix. Investigations at the Pondville Hospital indicate that the diagnosis of preinvasive cancer indicates that more biopsies should be made of various areas in the cervix. Thus, all but one of the preinvasive lesions were found to be true invasive cancer. Perhaps all that needs to be done for patients with preinvasive cancer is a total hysterectomy, but inasmuch as cure depends on radical removal, the Wertheim operation is not out of place. Schiller⁵⁵ and also Stevenson and Scipades⁵⁶ believe that early cancer grows slowly. The latter followed a woman with preinvasive cancer for eight years and one month, and the cancer finally became invasive. Another patient was followed for three years, and after death, serial sections of the cervix showed invasive cancer. It is probable that cancer in situ or preinvasive cancer cannot be considered as Bowen's disease, for that lesion remains intraepithelial. Knight⁵² states that it is not much like Bowen's disease. The use of radium in very early preinvasive cancer may be sufficient. Amputation of the cervix is not sufficient, for it does not remove all the endocervical epithelium. Total hysterectomy is therefore best; yet, as most cases show invasive cancer, perhaps the more radical Wertheim method should be advised.

To sum up, changes in the type of cervical epithelium are probably due to inflammation, yet it is not at all certain that such changes are not part of the picture of malignant change. Cancer in situ must be regarded in the light of our experience as early cancer, and the proper treatment is either full radium or x-ray treatment or total hysterectomy, or, even better, the Wertheim operation.

CANCER OF CERVIX AFTER SUPRAVAGINAL HYSTERECTOMY

This problem of cancer of the cervix after supravaginal hysterectomy is a real one, and anyone seeing large numbers of cervical cancers is struck by the great number of such cases. These cases are of two kinds, those in which the operation is done at the time the cervical cancer is present, and those in which the cancer develops some years later. I have had under my supervision at one time 3 patients in whom supravaginal hysterectomy had been done when they had obvious cervical cancer. This is inexcusable and is due to lack of inspection and ex-

amination of the cervix at the time of operation. It is probable that these patients were bleeding and had fibroids, and that the abdominal operation was done and the uterus removed without preliminary inspection of the cervix in the lithotomy position. In other cases the cancer develops within three to six months postoperatively and was certainly present at the time of the operation, but was not recognized because it was so early or was present in the endocervix. This type of mistake is more excusable than the former, but in either, if the patient had had a total hysterectomy instead of a supravaginal hysterectomy, the results might have been better. In still other patients the tumor occurs from two to twenty-five years after the operation. It is pathetic to see such patients, for they believe that when they were operated on the uterus was removed. Surgeons leave the cervix behind because of the danger of morbidity, because of the possibility of interfering with sex activity and because they fear the more difficult operation.

With the advances in the knowledge of the operation and better preparation of the patient for it, there is no excuse for not removing the cervix. In certain cases—in bad-risk patients and in obviously difficult operations—the cervix may be left, but this should be the great exception and not the rule. In 1934, Gellhorn and Spain⁵⁷ stated that the danger of total hysterectomy is far less than that of cancer of the cervical stump. Von Graff,⁵¹ who reported 581 cases of this disease, believes that in 137 cases (23.5 per cent) it was present at the time of the operation and that the remaining cases would have been cured by total hysterectomy. He condemns "coning out" the cervix as not being sufficient treatment, since it leaves the squamous-cell epithelium on the outside of the cervix. Behney⁵⁸ believes that the chance of curing cancer of the cervical stump with radium is no less than that in corresponding classes of cervical cancer with the uterus left intact. Ward⁵⁹ agrees with his conclusions. It is the experience of our clinics that the treatment is not so efficacious because the canal of the cervix cannot be used as the source of the central radium applicator. The danger of fistulas, as all agree, is greater because the protection of the uterus is absent. It has been the custom in some clinics to do a vaginal cervicectomy in early cases of cancer of the cervical stump, and good results have been obtained, but if surgery is to be done in early cases, whether in the cervical stump or in the untouched uterus, the Wertheim operation with its radical removal of nodes and vaginal tissue is the procedure of choice. The percentage of cancer of the cervical stump among cervical cancers is 3 to 4 per cent in all clinics, — not a very great number, — but at the Pondville Hospital there have been over 100 cases. The sad thing about these cases is that if the total operation had been done, no patient would have developed cancer.

RELIEF OF PAIN

The treatment of pain in cervical cancer is usually limited to patients with advanced disease who are not likely to be cured. Cleanliness, frequent douching, changing of dressings and bed rest help a great deal. The use of acetylsalicylic acid (aspirin), codeine and narcotics is familiar to all, yet there are patients whose pain cannot be controlled by ordinary measures.

Sometimes x-ray treatment distributed over the area of pressure and invasion by the tumor is of value. There are, however, many advocates of the use of intrathecal injections of absolute alcohol (Todd⁶⁰). This method is undoubtedly satisfactory in some cases, but in the great majority if sufficient alcohol is injected to stop pain, some sort of interference with the function of the bladder and rectal sphincter takes place and weakness of the legs occurs. The length of the relief from pain varies from a few hours to a few months. Certainly in hopeless cases this method can be tried, but no guarantee can be made that the patient will obtain a satisfactory result.

The use of sympathectomy for control of pain has been advocated by Todd, who does a presacral sympathectomy. Others, among them Waterman,⁶¹ have reported success with this type of operation. Relief can be obtained from pain in the midline, but in most cases it is not satisfactory. Chordotomy has distinct possibilities, and unilateral or bilateral section of the arteriolateral columns is not an extremely formidable operation and may be carried out under local anesthesia. These patients lose the sense of pain and temperature but not that of touch; they are not paralyzed. In patients with severe pain and with not too advanced cancer who appear to be going to live for months this operation offers a great deal, but for patients who are near demise alcohol injections are just as efficacious. The trouble with the operation is that it is usually done when the patient is in extremis and is shortly followed by death. Its use in earlier cases gives results that are more satisfactory. The danger of interfering with the bladder and rectal sphincter is a real one, but the relief of pain in hopeless cases is well worth the risk.

CANCER OF CERVIX IN NULLIPARAS

Nulliparas constitute a fairly high percentage — from 5 to 12 per cent — of patients with cancer of the cervix. It is often impossible to state whether a married nullipara has ever miscarried, and in the unmarried patient the question of whether a pregnancy has occurred is often a difficult one to ask. Since cancer of the cervix does occur in nulliparas, pregnancy or labor is not essential for the development of the disease. Nulliparas may have had endocervicitis before the development of cancer and may have had an exposed endocervix, with irritation. The knowledge that cancer is not too

infrequent in nulliparas is important, so that a surgeon will not content himself with doing a supravaginal operation merely because the patient has had no children. Careful inspection of the cervix must be done before a supravaginal operation, and its removal with the uterus is far better. Inasmuch as many nulliparas have fibroids, and since cancer of the cervix is more frequent in patients with fibroids than in those with a normal uterus, removal of the cervix in such cases is essential!

CANCER OF CERVIX IN PREGNANCY

Keller⁶² reports 3 cases of cancer of the cervix among 4000 pregnant women. The patients had no symptoms, the tumor being discovered at biopsy. Danforth⁶³ found the frequency during pregnancy to be 0.03 per cent. There is no agreement whether pregnancy causes an abnormal rate of growth of the cancer. Miller⁶⁴ believes that it does, but quotes Wagner, Weibel, Meyer, Schweizer and others who believe that it has a retarding influence. Smith⁶⁵ states that pregnancy is detrimental to patients with unarrested malignant tumors. He thinks that the tumor growth may be retarded by the pregnancy but that it is accelerated afterward.

The mode of treatment of cancer of the cervix in the pregnant woman must be decided according to the size of the conceptus. Keller⁶² agrees with Brouha and Gosselin⁶⁶ that in the first half of pregnancy a hysterectomy should be done in operable cases and that radium should be given in inoperable ones. They advise against x ray treatment in the first half because of its deleterious effect on the fetus. They believe that in the second half radium is ideal and has but little effect on the fetus. They allow the pregnancy to go to term and do a cesarean section. Danforth⁶³ believes that labor may be dangerous and is occasionally impossible, and advises x ray and radium at once when the pregnancy is far enough advanced to allow viability. He advises termination of the pregnancy if full treatment is given, because of the danger to the child. Brouha and Gosselin⁶⁶ analyzed 39 cases, including 2 of their own. In 10 cases radium was given in the first half of pregnancy, and in 7 an interruption of the pregnancy occurred in one to five and a half months. Three patients went to term and gave birth to normal children. Twenty-nine had radium, in the second half of pregnancy, and in this group there were 6 miscarriages and 2 fetal abnormalities. Eight of the mothers treated in the first half of pregnancy died. Of those treated in the second half of pregnancy, 19 were traced and 9 were living and well. These writers conclude that since irradiation in the first half of pregnancy is dangerous to both mother and child, a hysterectomy should be done. In the second half radium should be given, and if a miscarriage occurs a hysterectomy should be done at once. Hurdon⁶⁷ gives the incidence of cancer of the cervix in pregnancy as 0.5 to 2.0 per cent. In her

clinic the percentage was 0.6 per cent. She cites Pankow as collecting 50 cases of carcinoma during pregnancy that he had operated on with a five-year survival rate of 42 per cent. Hurdon believes that the uterus should be emptied because spontaneous abortion occurs two to four weeks after radiation without complications. She warns of the possibility of injury to the germ plasma of the child whose mother's cervical cancer has been irradiated. She states that there may be danger of transmitting germ plasma defects. On the other hand, there are children who have been delivered following irradiation of their mothers who have arrived at school age without any apparent physical defect. Hurdon's summary of the treatment of cancer of the uterus complicating pregnancy is excellent, and is presented below.

If the cancer is discovered during pregnancy

If the cancer is operable and the child not viable

Radical excision (Wertheim) of the unopened uterus
The prognosis for the mother is comparatively good

Radium therapy. If not followed by abortion evacuate by abdominal hysterotomy or the child may go to viability and be delivered by cesarean section. The prognosis for the mother is favorable. Abortion usually follows and abnormalities are frequent among the children that survive.

If the cancer is operable and the child viable

Cesarean section followed by Wertheim's operation. The prognosis for the mother is unfavorable, there is a good chance of survival for the child.

Radium therapy preceded or followed by Cesarean section (according to the period of gestation). The prognosis for both mother and child is comparatively favorable.

If the cancer is inoperable and the child not viable

Radium therapy followed by delivery by abdominal hysterotomy (in accordance with religious principles, pregnancy may be allowed to continue, with delivery by cesarean section at or near term).

If the cancer is inoperable, and the child viable

Radium therapy preceded or followed by cesarean section (according to the period of gestation).

If the cancer is discovered at the time of labor, and the baby is alive

If the cancer is operable

If the presenting part is still in the uterus
cesarean section followed by Wertheim's operation

If the presenting part is through the cervix

Labor followed by radiation treatment (as soon as involution permits). Treatment may be begun by x ray therapy a few days after delivery, and in tracheotomy radium as soon as practicable. The beginning of treatment should not be delayed beyond the ninth or tenth day.

If the cancer is inoperable

If the presenting part is in the uterus
Cesarean section followed by radiation therapy

If the presenting part is through the cervix

Labor followed by radiation therapy (as soon as involution permits).

The following criticism of Hurdon's advice should be made. If the cancer is operable and the child viable, it is perhaps better to do a cesarean section and then give radium to the cervix, and six weeks later to operate by the Wertheim method. The huge veins, the large lymphatics, the soft tis-

sues and the obvious danger of the infected cervix suggest treatment with radium, sterilization of the cervix by radiation and later operation. In cancer discovered at the time of labor, radical surgery should not be done for cervical cancer at the same time as cesarean section, for the reasons given above. There have been 3 such cases in our clinics. The first patient, who had been pregnant for six months, was given radium. A cesarean section was done at eight months; then x-ray therapy was given and radium treatment was repeated. The patient died of extensive miliary metastases one year after treatment. The second patient was given radium in the sixth month of pregnancy and had a cesarean section in the eighth month. The baby died of hemorrhagic disease of the newborn, and the mother was given further radiation and has been alive and well for over five years. The third patient was six-months pregnant, with an early growth. She was given radium in the cervix, a cesarean section was performed six weeks later, and three months after that a Wertheim hysterectomy was performed. The patient is alive but has a ureteral fistula, which means later nephrectomy. She had no metastases in the lymph nodes and should do well. A transverse cervical cesarean section had been done, and this interfered with the dissection about the cervix at time of the Wertheim operation. In another such case, it would seem wiser to do the classic operation rather than the cervical.

Hurdon discusses 15 cases of pregnancy subsequent to involvement of the cervix with cancer. Spontaneous delivery occurred in 8 cases, and 1 patient was delivered by cesarean section. Abortions were induced in 2 cases, and were spontaneous in 3. One patient had three abortions before a normal child was born. One child was delivered by morcellation. All the living children were said to be healthy, both physically and mentally. There are no records of a second generation.

SUMMARY

The treatment of cancer of the cervix by radiation is at a standstill. Radium alone and combined with x-ray has given excellent results. It is now time to concentrate on early diagnosis by means of the vaginal smear, the colposcope and the Schiller test. The addition of surgical removal of the lymph nodes and the radical Wertheim's operation in favorable cases may produce better results.

Cervical cancer can be prevented only by total removal of the cervix by total hysterectomy when it is irritated, lacerated or suspicious.

Various problems of cervical cancer are discussed.

264 Beacon Street

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 30201

PRESENTATION OF CASE

A twelve-year-old mongolian girl entered the hospital because of vomiting and fever.

The patient was normally delivered at full term. The parents were normal. Development was slow, and she presented such a feeding problem that, at

with vomiting and diarrhea for several days. These cleared with a special diet. She remained in essentially good health until 4:00 a.m. on the day before admission, when she suddenly started to vomit. The vomiting was "explosive," and continued during the day; the vomitus consisted of "white curdy and buttermasses, stool-like, with no bile." There was slight watery diarrhea, which stopped by mid-afternoon of that day. Tenderness was elicited in the "lower intestine." The abdomen became distended. She developed fever and the white-cell count was 29,200, with 82 per cent neutrophils. The red-cell count was 3,840,000. She continued to vomit occasionally during the following night but was slightly more comfortable on the morning of admission. Distention of the abdomen and tenderness became marked, especially on the right. She was transferred to this hospital.

Physical examination showed a slightly cyanotic, underdeveloped, typical mongolian girl. The heart and lungs were negative. The abdomen was distended and tympanitic. Peristalsis seemed to be

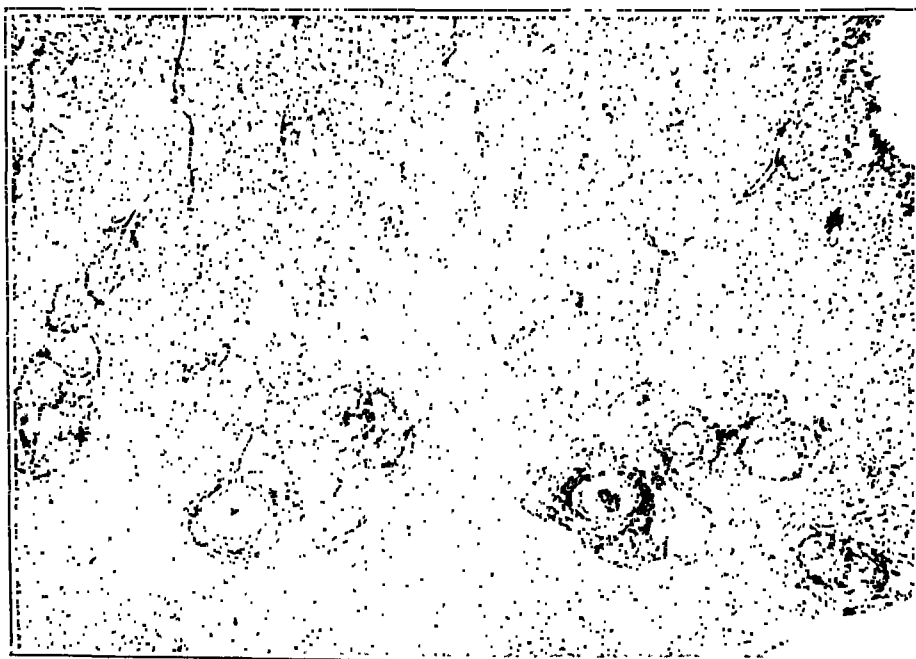


FIGURE 1. Photomicrograph of Kidney.

three, she was a seriously malnourished child. Dentition started at eight months, walking at nineteen months and talking at three years. She had measles and whooping cough as a child. At the age of six a diagnosis of mongolism was made, and about three years later she was placed in an institution. During the first year there she had recurrent ulcerations of the mouth, from which smears occasionally showed Vincent's organism. In the following two winters she had occasional episodes of "stomach upset,"

*On leave of absence.

depressed, and infrequent high-pitched sounds were heard. The liver was two fingerbreadths below the costal margin. The spleen was not enlarged. There was spasm on the left side of the abdomen. It was difficult to judge tenderness, but on one occasion the patient shrieked bitterly on deep palpation in the right lower quadrant. There were no masses. Rectal examination was negative.

The blood pressure was 155 systolic, 120 diastolic. The temperature was 101°F., the pulse 160, and the respirations 40.

Examination of the blood showed a white-cell count of 28,000. The urine contained occasional white cells, but was otherwise negative.

During the examination she became completely unresponsive and began to show peculiar gyrating motions of the arms. She became cyanotic, with an unusual mottled distribution. Rapid epileptiform convulsions began and persisted in varying degrees of severity for one hour. She was given 1 gm. of sodium phenobarbital and 10 cc. of paraldehyde. A lumbar puncture at the end of this time showed clear fluid, which contained 6 lymphocytes per cubic millimeter; the Pandy test was negative. Following this, she became irritable and irrational, thrashed about the bed and required restraint; 12 cc. of paraldehyde was given. About one hour later she suddenly threw herself on her face and vomited a slight amount of brownish material. The pulse was

I thought of the possibility of malrotation, with twisting and intestinal obstruction as a result. Most cases of malrotation, however, are seen relatively early in life, and it would be unlikely for a patient to reach the age of twelve and suddenly to develop such a condition. The only one that I can think of is a *volvulus of the cecum and ascending colon*, which I do not see how I can rule out.

Are there any x-ray films of the abdomen?

DR. BENJAMIN CASTLEMAN: No.

DR. LINTON: Another condition that should be considered is reduplication of the intestinal tract, which gives signs of intestinal obstruction; again, I cannot rule this in or out. One also has to consider a Meckel's diverticulum, which might produce intestinal obstruction owing to strangulation of the bowel around a fibrous band extending from the end of the diverticulum to the abdominal wall. Intus-



FIGURE 2. Photomicrograph of Heart.

irregular, with a rate of 30. Three minutes later, three hours after entry, no heart beat could be heard.

DIFFERENTIAL DIAGNOSIS

DR. ROBERT R. LINTON: We have here a typically mongoloid individual who entered the hospital because of an abdominal condition. Diagnosis is most difficult, since we have little if any evidence except the clinical examination and a very short history. In view of the high white-cell count one should consider an inflammatory condition, perhaps something that was obstructing the blood supply of the bowel, with secondary infection resulting from it. I believe, but I do not know, that congenital anomalies are not infrequently found in this condition. So one has to consider some of the congenital conditions that might produce vomiting, abdominal pain and distention and a high white-cell count. The temperature was 101°F. on one occasion.

susception is also something that one should consider, but I think that it can be ruled out, since 75 per cent of the cases of intussusception appear before the age of one. Another condition is an intra-abdominal herniation, as well as other congenital conditions that arise in the abdominal cavity.

I also thought of a peptic ulcer. Peptic ulcers with perforation do occur in children, but in view of the essentially negative past history I do not see how I can make a diagnosis of peptic ulcer.

There is another condition that I cannot rule out — appendicitis. The only thing against appendicitis is the sudden onset with an explosive type of vomiting, which is a peculiar way for appendicitis to manifest itself.

After running through the various possibilities I cannot make a definite diagnosis. I believe the likeliest was a *volvulus* of some portion of the intestine, interference of the blood supply, intestinal obstruction and peritonitis. The sudden death I

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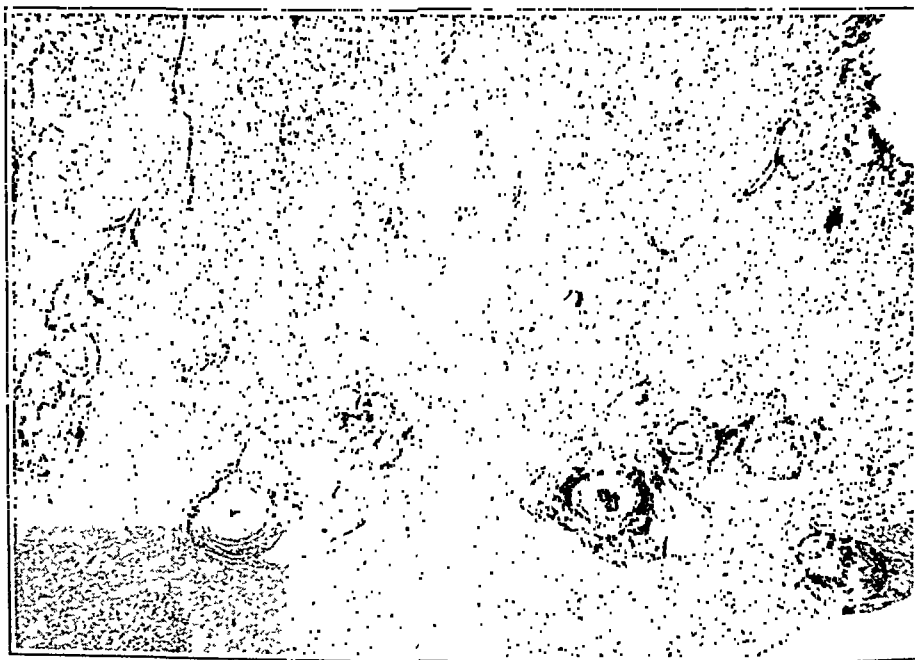


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The blood pressure was 155 systolic, 120 diastolic. The temperature was 101°F., the pulse 160, and the respirations 40.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy showed about a liter of turbid, hemorrhagic fluid in the abdominal cavity. The small intestine appeared red and gangrenous, and at the time of autopsy we thought that it had twisted and a diagnosis of volvulus of the small bowel was made. Microscopic sections, however, showed something extremely interesting, which perhaps accounted for the gangrene of the bowel.

In sections of the kidneys practically all the blood vessels, especially the medium-sized arteries, were diseased (Fig. 1). Many showed marked intimal proliferation, with practically no lumen; others had

tically complete destruction of the wall in some vessels (Fig. 4).

We have, then, a classic example of polyarteritis or periarteritis nodosa in a child of twelve, the youngest we have seen here. Involvement of the mesenteric vessels was the cause of the gangrene of the bowel. Lesions were found in practically every organ, including the brain, which may account for the convulsions.

DR. BUTLER: How sure is Dr. Benda that the child's blood pressure was normal?

DR. BENDA: According to the record in 1941 the blood pressure was 120 systolic, 70 diastolic. For a



FIGURE 4. Photomicrograph of Periadrenal Vessels.

marked cellular infiltrations around them. These perivascular cells were polymorphonuclears, plasma cells and eosinophils. In sections stained for elastic tissue, it was obvious that part of the elastica was completely broken, with fibrinoid necrosis of the wall. The intimal proliferation was apparently secondary to the disease in the wall.

The liver showed exactly the same process, with involvement of practically every vessel. In sections of the heart the coronary arteries were almost completely occluded by fibrous tissue (Fig. 2). Throughout the myocardium there were small areas of degeneration.

In sections of the adrenal glands, the surrounding fat showed vessels in all stages of the disease (Fig. 3); at one of the poles there was a small infarct due to the vascular change. On higher magnification, the periadrenal vessels showed extreme arteritis of all layers and also fibrinoid necrosis, with prac-

mongolian that seems to me slightly elevated, since they usually have a systolic pressure not higher than 100.

DR. CASTLEMAN: Have you seen this disease in children, Dr. Gross?

DR. GROSS: Dr. Butler probably remembers a case at the Children's Hospital that might be akin to this. The child was seven or eight years old and had marked arterial lesions, but not enough to give localized inflammation of the bowel and hypertension.

Addendum. Further inquiry into the patient's history after the diagnosis of periarteritis nodosa had been established disclosed that, twenty months before death, the patient had dysentery, for which she received over 600 gr. of sulfathiazole over a sixteen-day period. The sulfathiazole blood level was under 6 mg. per 100 cc., except for one day when it reached 12.6 mg. The white-cell count was 20,000,

with 80 per cent neutrophils, and the red-cell count was about 4,000,000. Many face eruptions and multiple abscesses developed and continued to be present for the following two months. The diarrhea recurred four months later, when she was given a total of 135 gr. of sulfadiazine over a four-day period. At that time a positive culture for the Sonne type of dysentery was obtained. The cultures were negative one month later. Four months later, about one year preceding death, she received sulfadiazine for only one day, probably not more than 30 gr.

In view of Rich's^{1,2} recent studies on the role played by sensitizing antigens, especially sulfonamides, in the production of periarteritis nodosa, it is not unlikely that the patient in this case, while under sulfonamide therapy, developed acute arterial lesions, which at autopsy a year later showed various stages of healing.

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CASE 30202

PRESENTATION OF CASE

A fifty-seven-year-old housewife was brought into the hospital because of pain in the left upper quadrant.

The patient was in apparent good health until six hours before entry, at which time she fell from the piazza of her home to the ground, a drop of six feet. She apparently landed on her left side and experienced severe pain in the left upper quadrant and left shoulder. She was able to stand up, however, and walked into the house, but she did this with considerable effort because of the pain. After sitting down in the house for a few minutes she felt "shaky," and during the next two or three hours had three attacks of vomiting. What the vomitus consisted of was not noted. The vomiting and deep breathing increased the pain in the left upper quadrant. There was no pain in the chest, no loss of consciousness, no loss of blood from any orifice, and no bowel movement.

The past history was negative except for an admission into the hospital some months previously for drainage of a carbuncle of the neck.

Physical examination showed a well-developed, rather obese woman who was complaining of pain in the left upper quadrant. The heart and lungs were negative. There was tenderness on pressure over the lower ribs, but no crepitus, or pain on inspiration. Marked tenderness was elicited in the left upper and lower quadrants, but none in the costovertebral angles. A nontender, movable mass twice the size of a grapefruit was palpable in the left lower quadrant, which on pelvic examination seemed

to arise from the left vault. This mass had been felt at the time of the previous admission.

The blood pressure was 100 systolic, 60 diastolic. The pulse was 70. The temperature and respirations were normal.

Examination of the blood showed a red-cell count of 4,560,000, with 80 per cent hemoglobin. The white-cell count was 24,000. The urine contained occasional white cells and innumerable red cells.

X-ray examination of the chest showed no evidence of fracture or pneumothorax. An intravenous pyelogram revealed the kidney outlines to be normal. The dye appeared in good concentration, outlining nondilated urinary passages, and no evidence of extravasation of dye into the soft tissue was seen. Plain films of the abdomen showed the pelvic mass already described.

Two abdominal taps were negative. The patient was given $\frac{1}{8}$ gr. of morphine and ice packs over the left quadrant. In the course of the next few hours the blood pressure rose slowly and the pain subsided. She was kept under close observation. In the course of the next two days the shoulder pain completely disappeared and the tenderness in the left upper quadrant practically disappeared. She was voiding well, but the urinary sediment still contained 20 to 25 red cells. Bowel movements were normal, and there was no vomiting.

On the fourth hospital day she had minimal pain in the left leg, with some swelling about the medial aspect, and there was a slight transient rise of temperature, which subsided. The next day, examination was entirely negative except for the persistent mass in the pelvis. The urine was clear, and a gastrointestinal series was negative except for a small amount of fluid in the left costophrenic angle.

On the seventh hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. ARTHUR W. ALLEN: Perhaps we might look at the x-ray films.

DR. MILFORD SCHULZ: There is nothing here except that which is confirmatory of the statements in the protocol. This film of the abdomen demonstrates the mass rising above the iliac crest. The pyelogram shows good kidney function, and I see nothing to suggest damage to the kidney.

DR. ALLEN: Does the mass change the course of the ureter in any way?

DR. SCHULZ: It is difficult to say that it does not displace it anteriorly, but it does not displace it laterally, in so far as it can be traced.

DR. ALLEN: Does the mass go into the pelvis?

DR. SCHULZ: I cannot see the lower margin where it merges with the pelvic shadows. Its lowermost reaches cannot be definitely determined.

This film of the chest and ribs shows nothing unusual. The shadow of the spleen cannot be outlined.

Dr. ALLEN: In the gastrointestinal series there is mention of a small amount of fluid in the left costophrenic angle. Can you point that out?

Dr. SCHULZ: That probably was a fluoroscopic observation; it cannot be seen on these films with any degree of certainty.

Dr. ALLEN: We assume that, at the time of this woman's first admission, a diagnosis was made regarding the pelvic tumor — that is, some note must have been made about it because it was recorded in the physical examination. It is not stated, however, whether she had been given a house appointment to have something done about it. I assume that she had been told that it would be a good idea to come back at least for examination and possibly to have this tumor removed. Obviously it was not considered to be malignant; otherwise she would have been followed and probably brought back to the hospital earlier.

We come down then to the present illness, which started with a fall, not from a great height to be sure, but far enough to cause considerable damage. The fact that she had pain in the left upper quadrant and pain on pressure over the lower ribs is consistent with the red cells found in the urine; in other words, she probably had a contusion of the kidney. The intravenous pyelogram rules out a serious injury to the kidney, because if the kidney itself had been fractured, there would have been some extravasated dye around the kidney when the pyelogram was made. The fact that she showed a considerable number of blood cells in the urine for three or four days after injury is, I believe, sufficient evidence to prove that she did have a contusion of the left kidney. It is difficult for me to connect the contusion of the kidney and the pelvic tumor, and I am going to assume that the two lesions had nothing to do with each other, that the accident did not produce a hematuria from the standpoint of the tumor, and that the pelvic tumor was an incidental finding and was not a factor in the acute illness.

Two interesting observations make one speculate about the region of the injury. One is the white-cell count of 24,000. I assume that that was repeated and confirmed. A contusion of the kidney will not give a white-cell count of that height, nor will a great many other acute injuries, except injury to the spleen. If a patient has had an abdominal injury and has a white-cell count above 20,000 — it is frequently above 30,000 — one must be suspicious of an injury to the spleen. We do occasionally pick up a high white-cell count associated with other acute conditions of the abdomen, particularly mesenteric thrombosis and pancreatitis. The other day a patient arrived here with typical appendicitis and a confirmed white-cell count of 27,000. That is very unusual. But the high white-cell count six hours following an injury in the region of the spleen makes one suspicious that, in addition to the

contusion of the kidney, there might have been injury to the spleen.

There is another lead in the story that makes me think of the spleen. Obviously the residents who studied this patient thought of the possibility of intra-abdominal bleeding, because they tried twice to aspirate blood from the abdominal cavity, but both these attempts were unsuccessful and they quite rightly assumed that there was no intra-abdominal bleeding.

It is obvious from the record that, because of the high leukocyte count and the tenderness in the splenic region, they were suspicious that there might have been an injury to the spleen. Their suspicions were allayed, however, inasmuch as the patient got over her symptoms promptly and her white-cell count became lower.

It is quite possible, though, to have a fractured spleen that gives this picture at entry, the spleen having become tamponaded by omentum, so that there is a period of complete freedom of symptoms. We all know of a good many cases in which a fracture of the spleen temporarily stopped bleeding. A man injured on a football field, for instance, improves to such an extent that he is allowed to play a week later, only to have a burst of bleeding, at which time the correct diagnosis is usually made. A great many cases of delayed bleeding of the spleen have been recorded, particularly those by McIndoe*; and in one case a secondary hemorrhage occurred as late as twenty-eight days after the original injury. The other day in the ward I saw a boy of about twelve who had fallen on a picket fence on his left side five or six days prior to entry. At operation he had a well-tamponaded spleen, which was successfully removed. The spleen behaves differently from the other abdominal organs in that respect. Once hemorrhage has ceased from the liver, one can be reasonably sure that a secondary burst will not occur; but even though hemorrhage from the spleen has temporarily stopped, it is wiser to remove the spleen.

They do not tell us what operation was performed. I assume, however, that they did not explore this woman for the spleen. They probably assumed that all the trouble in the left upper quadrant was due to the contusion of the kidney. If the operation was done for the pelvic tumor and if they found no blood in the peritoneal cavity, they probably removed the pelvic tumor; but if they found blood, in spite of the two negative taps, they very likely investigated the spleen. If they found blood in the peritoneal cavity, I hazard the guess that they found the spleen fractured and tamponaded.

The diagnosis as I see it is a pelvic tumor of some sort. The patient was fifty-seven, which is between the age of fibroids, which occur most frequently in

*McIndoe, A. H. Delayed haemorrhage following traumatic rupture of spleen. *Brit. J. Surg.* 20: 249-268, 1932.

the fourth decade of life, and that of ovarian cysts, which occur either early or late in life. I assume that the chance that this was a fibroid is better than that it was an ovarian cyst. In the acute condition she had a contusion of the left kidney with hemorrhage, and I raise the question of the possibility of a fractured spleen as well.

CLINICAL DIAGNOSIS

Fibroid uterus or ovarian cyst?
Intra-abdominal trauma?

DR. ALLEN'S DIAGNOSES

Contusion of left kidney.
Fibroid tumor of uterus.
Fracture of spleen?

ANATOMICAL DIAGNOSES

Ruptured spleen.
Uterine leiomyomas.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Dr. Allen predicted exactly how the men on the service reacted. They did operate with the purpose of removing the pelvic tumor. As soon as they got down to the peritoneal cavity, before opening it, they could see large bluish masses through the peritoneal coat, so they realized that they would find blood in the abdominal cavity and forgot about the pelvic mass. On opening the abdominal cavity they found about 500 cc. of clotted blood, and in removing some of that they discovered that the source of the bleeding was the spleen, which had been covered with omentum and

tamponaded, just as Dr. Allen prophesied. After the spleen and all the blood had been removed, exploration of the pelvis showed that the mass was composed of two large pedunculated fibroids, which it was decided not to remove at that time.

The spleen contained two jagged tears—one about 7 cm. in length, extending in for about 1 cm., and the other about 4 or 5 cm. in length, extending into a large cavity filled with blood. On cutting the spleen another large hemorrhagic extravasation was noted, without apparent connection with an external rupture.

Do you think, Dr. Allen, that during the fall the pressure of the fibroids might have helped injure the spleen? I suppose it would have been more likely if the fibroids had been calcified.

DR. ALLEN: I had not thought of that. I had assumed that the tumor was not large enough to play a role. Possibly such was the case. It does not take much more of a blow than this woman had to fracture the spleen. If she landed just right, the fall could have done it without any help from the fibroids.

I was much intrigued by the statement in the history about the fluid in the costophrenic angle that the radiologist saw in the fluoroscopic examination; it apparently does not show on the films. If that was true, it is good evidence that there was hemorrhage from something in that region, and the usual source would be the spleen.

DR. SCHULZ: The reason that we do not see evidence of fluid on the films is, I believe, that the patient was prone or supine when the films were taken and in the upright position when fluoroscoped.

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RECONDITIONING PROGRAM

THE battle of Waterloo, history tells us, was won on the playing fields of Eton, so much did the courage and discipline of his young officers contribute to the morale of Wellington's army. In a different sense, some of the future victories of our present war may have been won already on the football field of Harvard, for it is his practical experience in the reconditioning of athletes that has placed Colonel Augustus Thorndike, of Boston, formerly surgeon to the Harvard football team and more recently commanding officer of the 105th General Hospital, as director of the Reconditioning Division, created last year by the Surgeon General.

A program for this reconditioning of disabled soldiers, according to an editorial in the April 1 issue of the *Journal of the American Medical Association*, was given impetus in a two-day conference recently held at the Schick General Hospital, Clinton, Iowa, at which time the results of such a program, carried out for several months past, were demonstrated by the commandant, Colonel Dean F. Winn, and his staff.

Training for men to be returned to military duty or to be restored as quickly as possible to useful civilian occupations includes "physical reconditioning, educational reconditioning and emotional reconditioning." Physical exercises of the convalescent wounded are begun at the earliest possible time, and are based on a graduated system of calisthenics, drills, games and military training. At the same time, carefully planned programs for educational and emotional reconditioning are carried out by other well-trained personnel. In a nation whose able young manhood has almost entirely gone into the armed services, that irreplaceable segment of the population must be husbanded and guarded as the very strength of the country.

In an earlier stage of our supreme military effort, when we first began to gather our armies together and the lists of the rejected grew, emphasis was placed first on rehabilitation of the unfit, and then on prehabilitation—the correction of defects before examination, in order to minimize the number of rejections. This conservation of our effective manpower must continue, but as our forces gain battle experience, the inevitable shift must take place in favor of the salvaging of those whom battle has disabled.

More than ever before, great numbers of the disabled will be returned to full duty, others with invaluable battle experience will be made available for limited service and the majority of the remainder, it can be confidently expected, will find their places in useful civilian occupations.

CUTANEOUS SULFONAMIDE HYPERSENSITIZATION

THE indiscriminate employment of local applications of sulfonamide preparations on cutaneous manifestations is creating a menace of consid

proportions. Not only have many cases of contact dermatitis with extensive exacerbations of the original process been produced by such applications, but serious generalized reactions have been provoked. These preparations are being used widely, both by physicians and by laymen, for eruptions without regard to whether or not they are of bacterial origin, and the number of cases with an unfavorable reaction is increasing.

Although the figures thus far presented indicate that evidences of hypersensitivity develop in only 5 per cent of those in whom such local applications have been employed,¹ in the aggregate a great amount of disability, sometimes protracted, is being produced by the complications of sulfonamide therapy. Reports presented in the literature²⁻⁴ indicate that hypersensitization to these drugs may be general as well as cutaneous and may be occasioned in some cases by previous oral administration, and in others by the local application of sulfonamide preparations to the skin. After this sensitization is once produced, a recurrence of the cutaneous or of the general disturbance may be precipitated either by oral administration or by local application to the skin, and it is well recognized that this hypersensitivity may be permanent. Thus the local use of sulfonamide preparations introduces a definite hazard to the later administration of sulfonamide preparations internally, perhaps for pneumonia, peritonitis or other serious infection.

Although the original cutaneous disturbance may be exaggerated by the use of a sulfonamide, it is often not recognized that the drug is the causal factor in such a flare-up, with the result that it is continued and the convalescence considerably prolonged. Furthermore, some of these patients may become sensitized to other therapeutic agents, to occupational factors or perhaps to bacteria or bacterial products, as well as to the sulfonamides. Some cases are reported to be accentuated by exposure to actinic rays, and even after the skin has become normal, subsequent exposure to sun may reactivate the cutaneous disturbance. Activation may even occur following fractional doses of roentgen rays.

These cases of hypersensitization have become so numerous and the possible consequences so dis-

turbing that the Section on Dermatology and Syphilology of the Medical Society of the State of New York at its last meeting passed resolutions "strongly disapproving the indiscriminate use of sulfonamide drugs in relatively harmless diseases of the skin which can be satisfactorily treated by equally efficient drugs" and "condemning the use of prepared dressings containing sulfonamide drugs which are sold promiscuously." Shortly after these resolutions, the *New York State Journal of Medicine* commented editorially on the matter,⁵ emphasizing the necessity of preventing or reducing to a minimum such reactions of the sulfonamides.

Cole⁶ has recently reviewed the subject; he advises that "sulfonamides should not be administered locally for more than five days because of the danger of sensitizing the individual and perhaps later precluding internal sulfonamide therapy where the situation may involve a far graver disease."

Still more recently, Tate and Klorfajn⁷ cite the British experience with sulfonamide hypersensitization. These authors indicate that dermatitis is apt to appear within fourteen days after beginning the application of sulfonamide preparations, that the person so sensitized has a group sensitivity to the various sulfonamide drugs, that there is an apparent allergy to sunlight following such a dermatitis and that desensitization can be achieved. In one case in which desensitization was attempted, the extreme hypersensitivity is shown by the fact that "when the [oral] dose was increased to 1/250 grain daily the eruption began to break out afresh." In another previously reported case the oral administration of 1/8 grain was followed in six hours by an eruption similar to the earlier rash. They advise that topical sulfonamide therapy "should be reserved strictly for cases where withholding it might endanger life or lead to deformity." Editorial comment in the same issue of the *Lancet* supports earlier conclusions that these drugs should not be used for eczematous subjects, should not be applied to any condition for longer than a week, and should be much restricted in use.

Thus, growing experience with the local use of sulfonamide preparations demonstrates that these agents should be used as topical applications only

on the advice of a physician, who should prescribe them with great care and for a short period. Furthermore, the risks of indiscriminate use should be widely publicized.

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MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BARRETT—James A Barrett, M.D., of New Bedford, died April 28. He was in his fifty-ninth year. Dr. Barrett received his degree from the Maryland Medical College, Baltimore, in 1910. He was a member of the Massachusetts Medical Society, the American Medical Association, the New Bedford Medical Society and the New England Rheumatism Ray Society. His widow, a son and a daughter survive.

BULFINCH—George G Bulfinch, M.D., of Brookline, died April 14. He was in his ninety-sixth year. Dr. Bulfinch received his degree from Harvard Medical School in 1874. He was a member of the Massachusetts Medical Society and the American Medical Association. A son, three grandchildren and one great grandchild survive.

COCHRAN—John J Cochran, M.D., of Natick, died May 1. He was in his forty-eighth year. Dr. Cochran received his degree from Harvard Medical School in 1923. He was a counselor for the Middlesex South District Medical Society and a member of the courtesy staffs at the Newton and Framingham hospitals. He was a member of the Massachusetts Medical Society and the American Medical Association. His widow, two sons and two brothers survive.

CURTIN—John J Curtin, M.D., of Waltham, died March 10. He was in his sixty-first year. Dr. Curtin received his degree from Harvard Medical School in 1903. He was a member of the Massachusetts Medical Society and the American Medical Association. His widow survives.

FAILLACE—Gaetano Faillace, M.D., of Brookline, died February 19. He was in his seventy-second year. Dr. Faillace received his degree from the University of Naples Medical School, Italy, in 1903. In 1920 he was decorated by the Italian government for outstanding professional services among Italians in Boston and New England. He was a member of the Massachusetts Medical Society and the American Medical Association. His widow, two daughters and two sons survive.

GILLESPIE—Norman W Gillespie, M.D., of Dorchester, died April 28. He was in his fifty-sixth year. Dr. Gillespie received his degree from Harvard Medical School in 1915. He served at the Beverly Hospital, Boston City Hospital, Children's Hospital, Boston Lying-in Hospital, Walter Reed Hospital. He was a member of the Massachusetts Medical Society and the American Medical Association. His widow and two daughters survive.

JOHNSON—Herbert S Johnson, M.D., of Stoneham, died April 29. He was in his eighty-ninth year.

Dr. Johnson received his degree from Harvard Medical School in 1883. From 1897 to 1918 he practiced medicine in Malden, during which period he was a school physician and on the staff of the Malden Hospital. In 1918, he gave up private practice to join the staff of E. I. Patch Company, manufacturers of pharmaceutical supplies. He retired in 1932. He was a former member of the Massachusetts Medical Society.

A daughter and two sons survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

DISTRIBUTION STATIONS FOR ANTIPNEUMOCOCCUS AND ANTIMENINGOCOCCUS SERUMS

Because of continued reductions in the demand for antipneumococcus and antimeningococcus serums, and the necessity of eliminating nonessential processing and distribution services for the duration of the war, the number of distributing stations for the above products has been reduced. The following three classes of stations will be maintained hereafter:

1. Stations regularly supplied with antimeningococcus serum and with antipneumococcus serum of the types indicated.

CITY	STATION	SERUM
Boston	Bacteriological Lab., State House	Antipneumococcus serum (Types 1, 2, 4, 5, 7, 8, 9, 14 and 18) Antimeningococcus serum
Worcester	Worcester City Hospital Board of Health	Antipneumococcus serum (Types 1, 2, 4, 5, 7, 8, 9, 14 and 18) Antimeningococcus serum
Holyoke	Providence Hospital	Antipneumococcus serum (Types 1, 2, 4, 5, 7, 8, 9, 14 and 18) Antimeningococcus serum
Haverhill	Hale Hospital	Antipneumococcus serum (Types 1, 2, 5, 7 and 8) Antimeningococcus serum
New Bedford	St. Luke's Hospital	Antipneumococcus serum (Types 1, 2, 5, 7 and 8) Antimeningococcus serum
Pittsfield	House of Mercy Hospital Sampson Memorial Hospital	Antipneumococcus serum (Types 1, 2, 5, 7 and 8) Antimeningococcus serum

2. Stations supplied with emergency stocks of antimeningococcus serum and of antipneumococcus serum (Type 1), when adequate amounts of these serums are available.

CITY	STATION
Ayer	Community Memorial Hospital
Brookton	Brookton Hospital
Gardner	Henry Heywood Memorial Hospital
Greenfield	Franklin County Hospital
Hyannis	Cape Cod Hospital
Nantucket	Nantucket Cottage Hospital

3. Stations supplied with antimeningococcus serum in certain communities not listed above, where the demand for antimeningococcus serum has been relatively frequent. The appropriate stations will be provided with this serum for emergency stock so long as sufficient serum is available and the demand is in the community.

WAR ACTIVITIES

INDUSTRIAL HYGIENE

INDUSTRIAL EYE-HYGIENE PROGRAM

The Industrial Hygiene Division of the United States Public Health Service, in co-operation with the offices of the National Society for the Prevention of Blindness, — the Joint Committee on Industrial Ophthalmology and Otolaryngology, — has been developing and carrying out a program in eyesight protection in industry. Assistant Surgeon Joseph Lo Presti was detailed to the National Society for the Prevention of Blindness in New York City in July, 1943, for this purpose.

In the past, work in this field for the most part has been directed along eye protection and safety lines. The equally important aspect of this broad field, visual job analysis, has not received the study or emphasis that it warrants. By job analysis is meant the correlation of visual skills or abilities of employees, with job performances based on various criteria, such as speed of learning rate of work, accuracy of work, amount of spoilage, absenteeism and accident proneness or frequency. In addition, no serious attempts have been made in the past to establish minimum visual requirements for different types of occupation. For these reasons the scope of the industrial eye-hygiene program was made broad enough to encompass and emphasize these aspects — in fact, to include all important aspects of vision in industry.

Because of the acute shortage of ophthalmologists and allied professional groups engaged in eye care and eye service, other methods of visual examination had to be adopted to reach a sizable number of the industrial population. Three so-called "screening devices" were found to be already available, one of which is still in the experimental stage of its development. In order to evaluate the reliability of one of these devices, namely, the Ortho-Rater, a study was conducted at Stevens Institute, Hoboken, New Jersey. A group of 336 first-term students enrolled in the drafting course were tested by means of a simplified clinical procedure and by the Ortho-Rater. From five to six minutes per subject was taken for the examination. Data from this study are now in the last stages of analysis and it may be tentatively concluded that this screening device can be practically employed in industry to study visual skills. A visit was also made to the Visual Institute at Purdue University, Lafayette, Indiana, where the Ortho-Rater was developed. Methods of obtaining vision data and correlating them with job performance were studied with a view to adopting some of them in field work.

A comprehensive industrial visual survey is now being carried out in Connecticut, operating through the Bureau of Industrial Hygiene, Connecticut State Department of Health. The objectives of this project are: to obtain a cross section of industrial vision practices in a typical, concentrated industrial region engaged largely in war work; to compare various methods of examination, particularly screening tests, for vision; to derive recommendations for methods of appraising and improving existing visual conditions of employees and to select plants that may serve as a pattern to be followed throughout the country. Six plants have been thoroughly studied to date in the Hartford region, the work being conducted through the medical department of each plant. Whenever practical, employees were tested by various screen procedures, including the Ortho-Rater and the Vector-graph; and, on one occasion, with the Telebinocular, data on visual acuity (distance and near) muscle balance, vertical and lateral (distance and near) color vision, depth perception (stereopsis) were obtained. In addition, the Industrial Eyesight Protection Appraisal Form (Publication No. 402B — National Society for the Prevention of Blindness) was filled out for each plant covered, after consultation with the person responsible for the eye program in the plant. Items checked on this form include:

Employee Data: General medical supervision and special provisions made for eye services; safety items; first-aid facilities; other special eye services, such as screening, periodic recheck and examination for particular exposures; and provision for supplying eye appliances.

Plant Job Data: Illumination, eye hazards and provision for eye safety and protection.

This appraisal form will be sent to at least 30,000 industries by the War Production Board. In line with this survey, and anticipating that industry will seek ophthalmologists to assist in correcting conditions that

may be found, the National Society for the Prevention of Blindness, with the co-operation of the chairman of the Joint Committee on Ophthalmology of the American Medical Association, is planning a seminar on industrial ophthalmology to be held in New York City at an early date. It is hoped that this will bring forcibly to the attention of the management of industries the need for an adequate eye conservation program. — Reprinted from *Industrial Hygiene News Letter* (March, 1944).

CORRESPONDENCE

MIDDLESEX UNIVERSITY SCHOOL OF MEDICINE

To the Editor: Dr. Stephen Rushmore in a letter published in the March 2, 1944, issue of the *Journal*, states that "the background of the discussion" with the Council on Medical Education and Hospitals of the American Medical Association regarding the status of Middlesex University School of Medicine is characterized in the following quotation: "The Council did not feel justified in offering any approval or even encouragement in connection with your efforts." Removed from the context of frequent discussions held by the Council with Dr. Rushmore, this sentence gives an entirely erroneous impression of the attitude of the Council.

The implication of this reference and the remainder of Dr. Rushmore's letter is that the Council is concerned with factors other than the quality of instruction in considering a school for inclusion on the list of approved medical schools, and that the Council desires to avoid additions to this list partly by refusing aid and encouragement to new schools.

Aid and encouragement have repeatedly been given to developing medical schools by the Council. Within the past year the medical school of the Southwestern Medical Foundation and the Bowman Gray School of Medicine have been approved as four-year schools. The University of Utah has expanded into a four-year medical school and partly through the help of the Council gives every promise of developing an excellent program. There has been extended correspondence with state authorities and conferences in Alabama with regard to their new four-year school. Correspondence and conferences are also being held with at least three other groups in which encouragement, advice and aid have been given by the Council.

It is notable that in each of these instances the school seems to have well-conceived plans and reasonably adequate financial and other resources and shows promise of meeting at least the minimum standards of medical education.

It is the Council's responsibility and privilege to give aid, advice and encouragement to such situations. It is clearly also the Council's responsibility not to encourage ill conceived or inadequately supported ventures into medical education. The Council has had to assume this responsibility on more than one occasion in the past and will continue to do so in the future when necessary.

VICTOR JOHNSON, M.D., *Secretary*
Council on Medical Education and Hospitals
535 North Dearborn Street
Chicago 10

OLD NAVAL MEDICAL COMMISSIONS

To the Editor: The National Naval Medical Center, of Bethesda, Maryland, is endeavoring to collect for its archives a complete set of commissions issued to Naval medical officers and signed by past presidents of the United States.

There is a small nidus now at the Center, and it is hoped to be able to build this up to completion. Through the Navy Department Library and the National Archives a few more have been located. I am asking you to insert this letter in the *Journal* with the idea that various libraries or individuals may have in their possession such old commissions and would be willing to turn them over to the Center. If such are found and the owners are so generous, there could be no more fitting enshrinement of them than their use for this purpose.

ROBERT C. RANDELL
Commander, (MC) USNR
Division of Publications

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(Notices on page xvi)

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THE SURGICAL TREATMENT OF ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULAS*

WILLIAM E. LADD, M.D.†

BOSTON

ATRESIA of the esophagus with or without tracheo-esophageal fistula has been a baffling problem for the surgeon. If there is any surgeon who has attempted to save the lives of patients suffering from these malformations who has not had many disappointments and numerous trials and

In 1931 Rosenthal¹ reported 255 cases, in 1933 O'Hare² reported 281 cases, and by 1941 Ashley³ was able to collect 314 cases. From the records of the Children's Hospital in Boston can be added 72 cases, which brings the total close to 400. These figures make it apparent that atresia of the esoph-

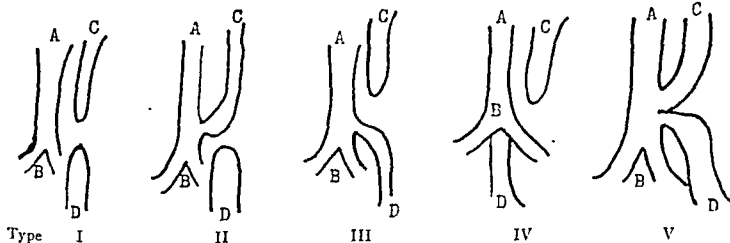


FIGURE 1. Diagram Showing the Arrangement of the Trachea and Esophagus in the Various Types of Esophageal Atresia and Tracheo-esophageal Fistula.

The letters refer to the following structures: A—trachea; B—bifurcation of trachea; C—upper segment of esophagus; and D—lower segment of esophagus.

embryology, I have not heard of him. Until very recent years this condition was considered incompatible with life. Obstetrician and pediatrician alike commonly advised that it was not worth while to attempt any remedial procedure. In the last few years, however, a few successes or partial successes have been reported from various parts of the country, and a correct point of view has been adopted: namely, that surgical intervention should be attempted. We have had a comparatively large experience with these cases at the Children's Hospital in Boston, and it may be of interest to relate our experiences in the surgical management of these anomalies.

In 1884, Mackenzie¹ attributed the first description of this condition to Durston (1670), and in 1821 Martin² published the first case report. In 1919 Plass³ reported 136 cases from the literature.

*From the Surgical Service, Children's Hospital, and the Department of Surgery, Harvard Medical School.
†The Rachford Memorial Lecture, presented before the Cincinnati Academy of Medicine, January 19, 1944.
†William E. Ladd, Professor of Child Surgery, Harvard Medical School; of Surgical Service, Children's Hospital.

agus is a much more frequent anomaly than it has usually been considered to be.

There are to be found in the literature various classifications of congenital anomalies of the esophagus. For the purposes of the present discussion, only those will be considered that have been seen in this series from the Children's Hospital. These cases may be divided into five types, as illustrated in Figure 1. Each type has minor variations. In Type I, the upper portion of the esophagus ends in a blind pouch in the region of the body of the first or second dorsal vertebra, and the lower segment of the esophagus begins again in a blind pouch at the level of the fourth or fifth dorsal vertebra. In Type II, the upper segment of the esophagus ends in a fistulous tract entering the trachea just above its bifurcation, whereas the lower segment is much the same as in Type I. In Type III, the upper segment ends blindly as in Type I, whereas the lower segment is connected to the trachea just above its bifurcation by a fistulous tract. This type and Type IV are by far the commonest in the reports.

of the literature as well as in our own experience. Type IV is similar to Type III except that the fistulous tract of the lower segment enters the trachea at its carina instead of just above its bifurcation. In Type V, both the upper and lower segments communicate with the trachea, as shown in the diagram. These types may be quite accurately diagnosed and are important to consider when one is deciding on his plan of treatment. For any form of treatment to be successful, it is of paramount importance to make the diagnosis as early as possible and to have the infant transferred to a hospital equipped to care for this kind of patient. This

without tympany, according to the variety of the malformation.

Obviously, in Types I and II there is no possibility for air to enter the stomach and intestines, so that one finds the abdomen sunken and without tympany. In Types III, IV and V, however, every time the infant breathes he forces air into the stomach and intestines. In these types, therefore, the abdomen is moderately distended and extremely tympanitic and sometimes contains large amounts of air if the tracheoesophageal fistula of the lower end of the esophagus is a large one.

With these symptoms and findings, the next step



FIGURE 2. *Atresia of the Esophagus, Type I.*

These roentgenograms were taken preoperatively. Note the complete absence of air in the stomach and intestine.

early diagnosis and allocation of the patient is usually the responsibility of the obstetrician or pediatrician.

The diagnosis may be suspected when the newborn infant has an excess of saliva in the mouth and perhaps an associated cyanosis. The next suggestive symptom to present itself is immediate vomiting after the first and any succeeding feeding. If the infant is not put to the breast or is not offered the bottle, he may appear quite normal after the excess saliva has been suctioned from the pharynx. Examination of the chest, however, usually discloses moist rales caused by aspiration of saliva or fluid given. These rales are apt to be most marked at the right apex, possibly for the reason that in the dorsal position aspirated fluid enters the right main bronchus and then the bronchus to the right upper lobe more easily than any other part of the lungs. Abdominal examination shows the abdomen to be either distended with air and tympanitic or completely flat

in the investigation is to insert a small rubber catheter in the esophagus. If this meets obstruction at 10 to 12 cm. from the lip margin, the diagnosis of esophageal atresia is practically confirmed. It is well, however, to check this finding by a roentgenologic examination to make sure that the catheter has not curled up in the pharynx or esophagus. The administration of barium is undesirable regardless of the type of malformation. If the case is of Type II or V with a fistula between the upper segment and the trachea, the administered barium goes directly into the lung and causes an aspiration pneumonia or an increase in the already existing one. The only reason for which a contrast medium is desirable is to determine the presence or absence of a tracheal fistula in the upper segment of the esophagus. To gather these data, a small amount of lipiodol should be used during a fluoroscopic inspection. If a large amount is used and it is not watched with the aid of the fluoroscope, some of it may spill over the top, so

to speak, be aspirated and confuse the picture. A roentgenologic examination of the abdomen is also of advantage in differentiating the varieties of the malformation. If this examination shows no air in the abdominal viscera, one must be dealing with Type I or II, if, on the other hand, the ex-

amination shows a serious nature and that some are even incompatible with life without relief by major surgical procedures.

TABLE 2 Site of Fistula in Cases of Types III and IV

SITE OF FISTULA	NO. OF CASES
At carina	16
Above carina	
0.0-0.5 cm	9
1.6-1.0 cm	3
1.1-1.5 cm	4
1.6-2.0 cm	2
Over 2.0 cm	1

It can also be stated, however, that there were 23 cases in this series with no accompanying malformations.

There is a considerable variation of the location of the fistulous opening into the trachea, as seen in Table 2 which lists the cases of Types III and IV.

TABLE 3 Distance between Esophageal Segments

DISTANCE	NO. OF CASES
Ends overlapping	1
0.0 to 0.5 cm	5
0.6 to 1.0 cm	7
1.1 to 1.5 cm	6
1.6 to 3.0 cm	4
3.1 to 3.5 cm	2
8.0 cm	1

Table 3 shows the variation of the distance between the two segments of the esophagus as noted in the post-mortem findings. This variation be-



FIGURE 3 Atresia of the Esophagus, Type III
Note the catheter in the blind end of the upper segment, the pneumonia at the right apex and the barium (unnaturally given) scattered through the lung. There is marked distention of the stomach and intestine.

When the examination shows the stomach and intestines filled with air, one can rest assured that one is dealing with Type III, IV or V. The careful records kept by Dr. Sidney Farber in the Pathology Department have made it possible to collect data that are not only of interest but of value in helping to formulate the plan of treatment.

From post-mortem findings it is apparent that these anomalies of the esophagus are frequently associated with anomalies of other parts of the body, as demonstrated by Table 1, which shows the type

TABLE 1 Anomalies Associated with Atresia of the Esophagus

TYPE	NO. OF CASES
Atresia or stenosis of the small intestine	3
Meckel's diverticulum	8
"	3
"	7
"	10
"	6
"	5
"	18

and number of other malformations that occurred in this series. It should be noted from a glance at this table that many of these anomalies are of a



FIGURE 4 Atresia of the Esophagus, Type II
Note the catheter in the blind end of the upper esophageal pouch, the pneumonia on the right and the marked distention of the stomach and intestine.

comes an important factor when one is considering the selection of the type of operation best suited for a given case.

These variations are not so important, however, as the two fundamental causes of death, which are pneumonia and starvation. Of these two, pneumonia is the more difficult to combat. Any operation that fails to prevent aspiration of saliva or fluid given either by mouth or by stomach is usually doomed to failure.

There have been numerous plans of surgical approach to this problem, some of which come close to meeting the requirements for combating these two main causes of death. The operation devised by Gage and Ochsner,⁷ which consists of tying off the cardia and doing a gastrostomy and marsupialization of the upper segment of the esophagus, has much to recommend it. It prevents the constant aspiration of secretion from the upper segment and allows feeding by gastrostomy without danger of reflux into the lungs through the tracheoesophageal fistula. Carter's⁸ objections to the operation are that it leaves a long esophageal pouch connected to the trachea and that the esophagostomy opening is too far removed from the gastrostomy. The first objection appears to be valid, since this pouch is certain to be a source of aspiration or infection at some later period. Our experience leads us not to concur with the second objection, since we have found that liquid and food pass through a long skin tube quite as readily as through a short one. We do, however, have another objection to the operation of Gage and Ochsner. This is that the ligature around the cardia may slough through and result in either leakage or recanalization of the esophagus. This catastrophe has indeed happened in 2 of our cases under a slightly different condition: namely, when the esophagus has been tied higher up in the mediastinum. To obviate leaving a long lower-segment pouch of the esophagus, Gamble⁹ devised an operation that has the obvious drawback of a permanent tracheal fistula. He tied off the cardiac end of the stomach and brought the esophageal end of the stomach connecting with the esophagus out onto the abdominal wall. Leven¹⁰ in 1936 advocated an operation embodying much the same principles as did that of Gage and Ochsner but with a different technic. He later abandoned this plan, which he had used with 2 patients, both of whom died of pneumonia.

Carter⁸ devised an operation that consisted of bringing the lower end of the esophagus down through the diaphragm and leading it up onto the abdominal wall. This was done through an abdominal approach. We have the same reason for objecting to Carter's operation that he himself uses against the operation of Gage and Ochsner: namely, the leaving of a long lower-segment pouch of the esophagus. It should also be noted that his patient died of pneumonia after eight to nine weeks of life. Regardless of his report that the pneumonia was an incidental development independent of the remaining esophageal pouch, it is still impossible to

believe that the presence of such a sac is desirable or without danger.

The next operative procedure to be considered is that of a direct attack on the site of the malformation through the back extrapleurally, tying off the tracheal esophageal fistula and marsupializing the ends of the lower and upper segments in the back. This plan was originally advocated by our former associate, Dr. Charles G. Mixter, and it was performed on several occasions by various members of the surgical staff of the Children's Hospital. One patient who was operated on according to a modification of this plan by my associate, Dr. Thomas H. Lanman,¹¹ survived for forty-seven days but eventually succumbed to pneumonia, pleuritis, mediastinitis and septicemia. This operative plan has some advantages; it leaves no blind esophageal pouch, takes care of salivary secretions and provides for feeding, and leaves open the possibility of a later end-to-end anastomosis. It has the disadvantages that the esophagostomy is in a position in which it is hard to handle and that it is difficult to prevent the development of mediastinitis, which has ultimately been a factor in the death of every patient in whom we have employed it. We have abandoned its use.

End-to-end anastomosis through an extrapleural approach in the back is without question the operation of choice in all patients in whom the two ends of the esophagus are close together. It closes the tracheoesophageal fistula, takes care of the salivary secretions, provides for feeding and theoretically restores the esophagus nearer to normal than does any other plan. The technical difficulties are three: the discrepancy in size of the two esophageal segments, the distance between the segments and the anatomic structure of the esophagus itself. The first two of these obstacles are variable according to the findings in each case. The third one is constant but should be surmountable provided that the other two factors present only minor difficulties. Until recently attempts by various members of the Children's Hospital staff at direct end-to-end anastomosis in cases of tracheoesophageal atresia have met with no success. Through a modification of our technic in suturing, the patients in 2 cases of direct anastomosis are doing well. The esophagus is reached by the same extrapleural approach that we have been using for the last four or five years for tying off the tracheoesophageal fistula. An L-shaped incision is made between the inner border of the scapula and the spine on the right side and run underneath the inferior angle of the scapula (Fig. 5). By this incision the third, fourth and fifth ribs are exposed in the back. A section of the fourth rib is excised subperiosteally, and the third and fifth ribs are cut to allow for retraction. The pleura is then stripped off the thoracic cage until the azygos vein is seen. One next identifies the communicating branch of the azygos vein, and it is tied and cut.

This acts, as a rule, as an excellent landmark for the esophagus. Both segments of the esophagus are then identified. The tracheoesophageal fistula of the lower segment is tied and cut. After the tracheoesophageal fistula has been eliminated and the lower segment of the esophagus has been mobilized, the upper end of the esophagus is likewise identified and mobilized, care being taken not to injure the

placed between them to invert the edges. The anastomosis thus having been completed, the ends of the ribs that have been cut are approximated. The periosteum of the rib that has been excised, is likewise sutured together, and the muscle layers of the back are reunited and the skin closed over a small drain that has been left in between the pleura and the thoracic cage. During the whole procedure the

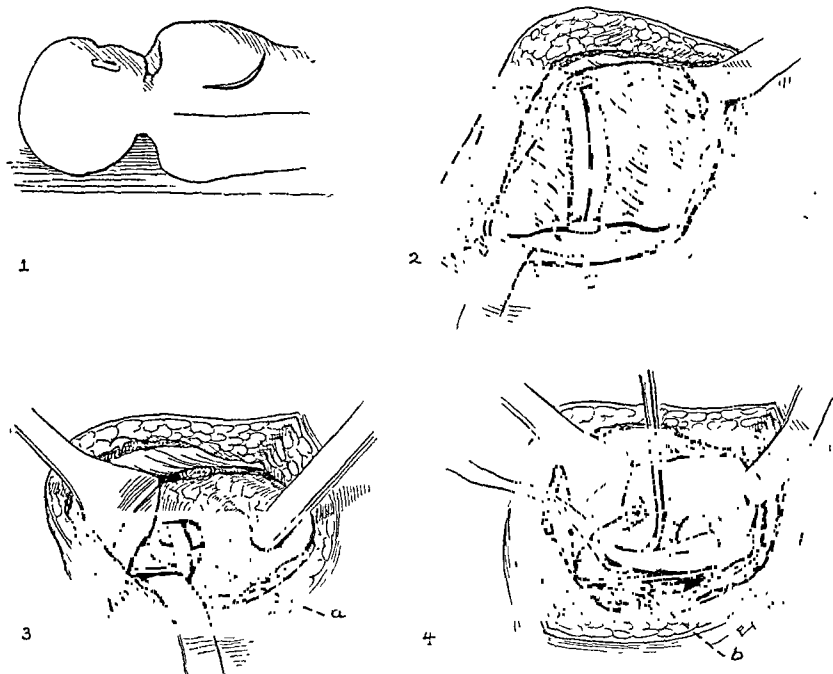


FIGURE 5. Operation for Direct Anastomosis of Esophagus.

shows the incision between the inner border of the scapula and the spine; 2 shows the third, fourth and fifth ribs exposed with section of the fourth rib excised subperiosteally; 3 shows the pleura and lung retracted and the communicating branch of the azygos vein (a) lying over the esophagus; and 4 shows the communicating branch of the azygos vein (b) cut, and the esophagus and tracheoesophageal fistula exposed and ready for tying and cutting.

neumogastric nerve. Four stay sutures are placed near the end of each segment, as shown in Figure 6. Each of these sutures starts about 1.5 cm. from the end of the segments of the esophagus. These four sutures are of great importance since they give a firm attachment to tissue, which is by nature a loose structure and allows ordinary sutures to pull out easily. The catheter, which has already been inserted in the upper segment of the esophagus, is run through the lower segment into the stomach and left there. One next uses four or five interrupted sutures to approximate the mucous membrane of each end of the esophagus. The four stay sutures are tied, and four interrupted mattress sutures are

pleura has not been opened and there is no problem of pneumothorax. This approach is preferable to that on the left side, which has been advocated by Haight and Towsley,¹² but whether one reaches the esophagus through the right or the left side at the back is a matter of preference and is of no great importance.

The patient is fed through the inlying catheter for a week or ten days, when a gastrostomy is performed and the esophageal catheter is removed. In the 2 surviving patients treated by this technic we have avoided the difficulties of a leak in the anastomosis, which was experienced by Haight in his successful case. Although this is the operation of choice in

selected patients in whom the two ends of the esophagus are close together, it is an extremely difficult operation and is probably unsafe in patients in whom the two ends of the esophagus are far apart.

As previously stated, it was apparent in our experience that pneumonia was the usual factor that prevented survival. It was also presumed that aspiration was the major cause of the pneumonia.

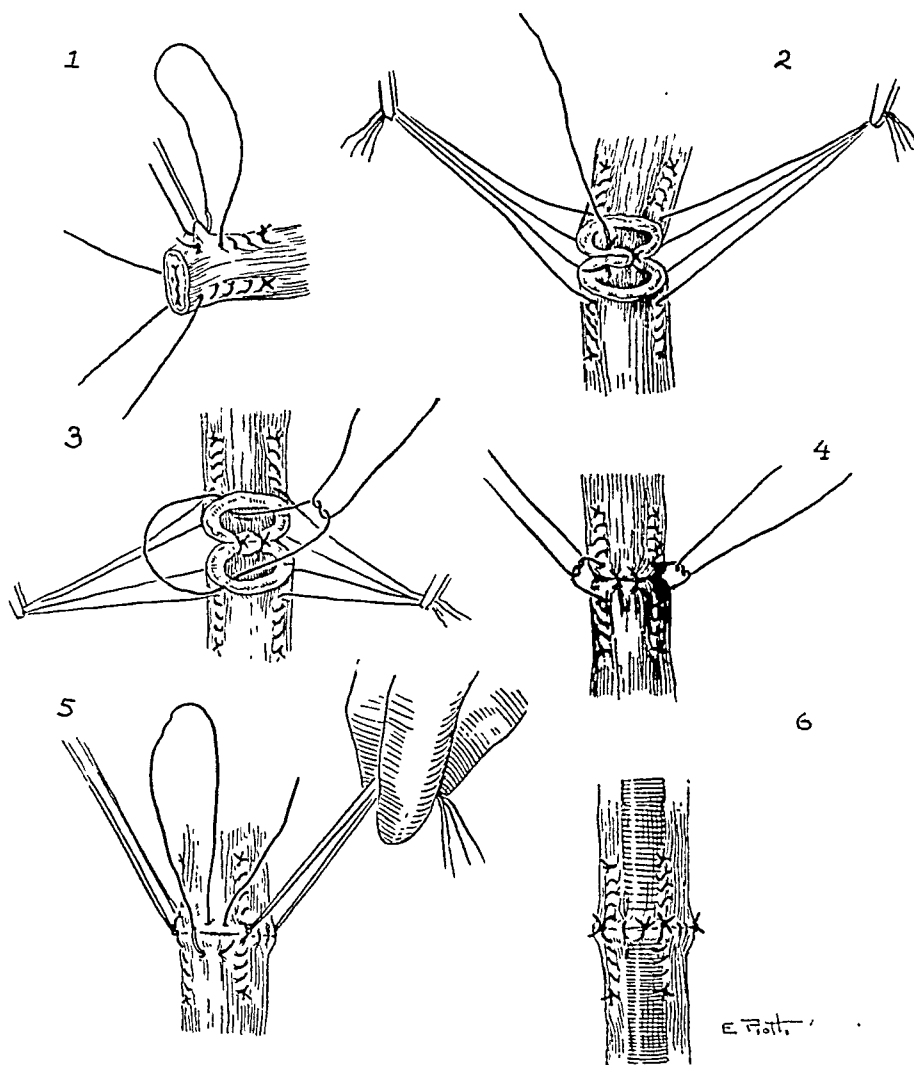


FIGURE 6. Operation for Direct Anastomosis of Esophagus.

1 shows the placement of the stay sutures; 2 and 3 show the two ends of the esophagus brought together by the stay sutures, and the placement of the interrupted sutures to the mucous-membrane sutures; 4 shows the completion of the mucous-membrane sutures, and the stay sutures being tied; 5 shows the method of placing the mattress sutures for the sake of inversion after the other sutures have been tied; and 6 shows the completed anastomosis with the inlying catheter running through it.

For these cases we have adopted a different technic, which we have been following for a little more than four years, with 8 patients now living.

It is interesting to note that Leven,¹³ at almost the identical time, came to the same conclusion about methods of attacking this problem and adopted principles identical with ours with only minor variations of technic. So far as I know, he has the oldest living patient with esophageal atresia and a tracheoesophageal fistula, his patient being twenty-four hours older than our oldest living one. In a recent personal communication he states that he has 4 additional patients living who have been operated on according to principles similar to those about to be described.

It therefore seemed logical to adopt a surgical plan that would have for its first objective the elimination of the conditions favoring aspiration. After this had been accomplished, the next step was to provide for feeding, and the third step was the construction of an anterior thoracic esophagus.

In patients with Types III and IV in whom the ends of the esophagus are too far apart to warrant an attempt at direct anastomosis, the esophagus again is approached in the same manner as just described for a direct anastomosis and the point of the tracheoesophageal fistula is identified. The fistula is then tied and cut. In some earlier cases only the tracheoesophageal fistula was tied, and in 2 cases the ties cut through the esophagus, the

esophagus was recanalized and the fistula was re-established (Fig. 7). One of these patients died from drowning after a gastrostomy feeding. In the other case it was recognized by the symptoms

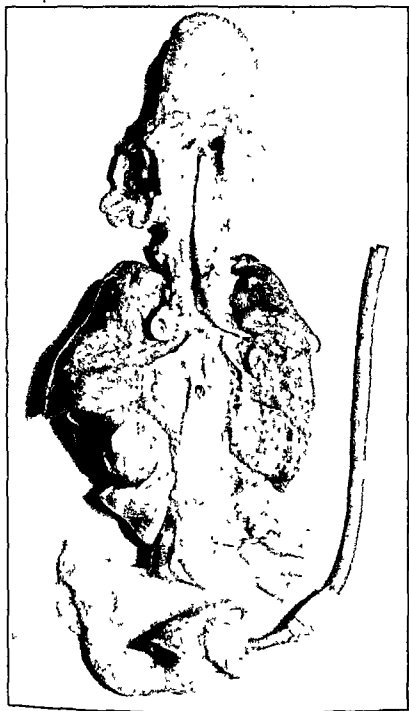


FIGURE 7. Post-Mortem Specimen Showing a Recanalized Esophagus.

The tie that was originally around the esophagus is within its lumen.

that the patient was in the same condition. The wound was reopened, the fistulous tract was cut and the ends were tied off. The patient is in the process of having his anterior thoracic esophagus constructed.

After the tracheoesophageal fistula has been obliterated by tying and cutting, the chest wound is closed as before. In a few days a gastrostomy is done, which allows feeding to be carried on successfully without the danger of the milk's being regurgitated into the lung. During this interval the patient is kept in a moderate Trendelenburg position and either continuous or intermittent suction is applied to the pharynx to prevent the aspiration of saliva.

The third stage of the operation consists of bringing the upper segment of the esophagus out in the

neck. This is accomplished by making a small transverse incision 1.5 cm. above and parallel to the clavicle, the inner end of the incision starting at the midline and the incision being carried laterally to the left for a distance of 3.5 cm. With the head extended and rotated to the right, the trachea is displaced laterally and does not interfere with the identification or freeing of the esophagus. In some cases, to give more room, the lower end of the sternocleidomastoid muscle is cut. There is usually a fibrous band extending downward from the lower end of the upper segment of the esophagus into the mediastinum. This must be cut in the mediastinum before the blind end can be delivered. After its delivery it is opened, the musculature of the esophagus is stitched to the subcutaneous tissue and the mucous membrane is approximated to the skin. The esophagostomy allows for the free discharge of saliva over the neck and avoids the danger of aspiration pneumonia.

After these procedures have been completed one can wait for an indefinite period before constructing the anterior thoracic esophagus. In our first successful case, considerable time was spent in trying to connect the esophagostomy to the gastrostomy by

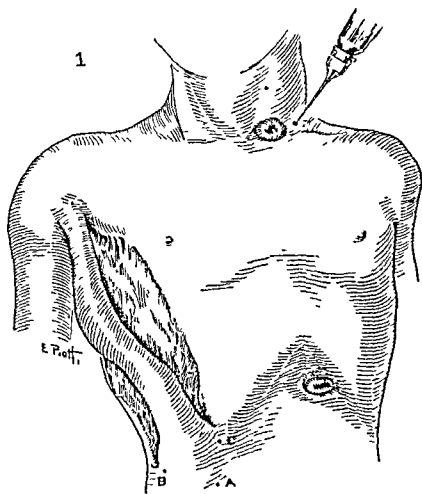


FIGURE 8. Fifth Step of the Operation in Types III and IV.

1 shows the tube graft with the Thiersch graft underneath it, and the marking of the skin around the esophagostomy for the transfer of the lower end of the tube graft (A, B and C).

various devices. Although this has been successfully done in adults, it was eventually abandoned as being impractical in infants.

The original gastrostomy in our oldest patient was changed to the Ssabanejew-Frank type and connected to the skin tube of the anterior thoracic

esophagus. In the next patient, now over two years old, the original gastrostomy, which was of the Witzel

method has consisted of making two parallel incisions, elevating the flaps of skin and suturing the

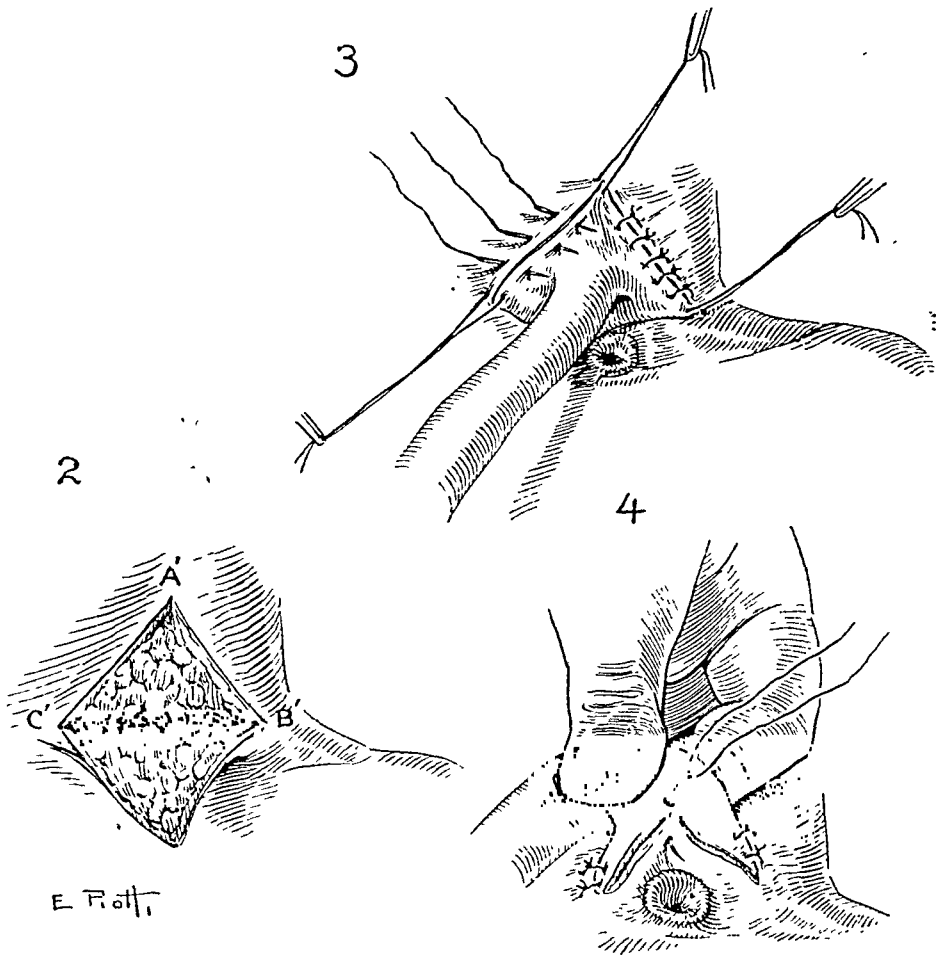


FIGURE 9. Fifth Step of the Operation for Types III and IV.

A V-shaped incision (A', B', and C') is made over the esophagostomy opening as shown in 2. The points A, B, and C, marked in Figure 8, are then sutured to A', B', and C', respectively. The flap that is turned down over the esophagostomy opening is sutured to the undersurface of the tube graft.

type, was closed and the whole of the lower segment of the esophagus was brought down through the diaphragm and out of the abdominal incision onto the chest wall. This was done in two stages. The first stage consisted of the freeing of the esophagus by an extrapleural approach through the right side of the back. The second stage was a laparotomy, during which the cardiac end of the stomach was freed and the lower segment of the esophagus was brought down through the esophageal hiatus and out of the abdominal incision. This segment was next tunneled under the skin of the chest, brought out through a suitable-sized incision and stitched to its skin edges. This procedure is much like that recommended by Carter⁸ except that no segment of the esophagus is left in the mediastinum. Although we have a patient still living who was operated on two years ago by this plan, its use has been abandoned on account of the difficulty of regurgitation.

The next problem is the construction of the skin tube and the establishment of the continuity of the esophagus with the stomach. This has been done in several ways by different surgeons. The simplest

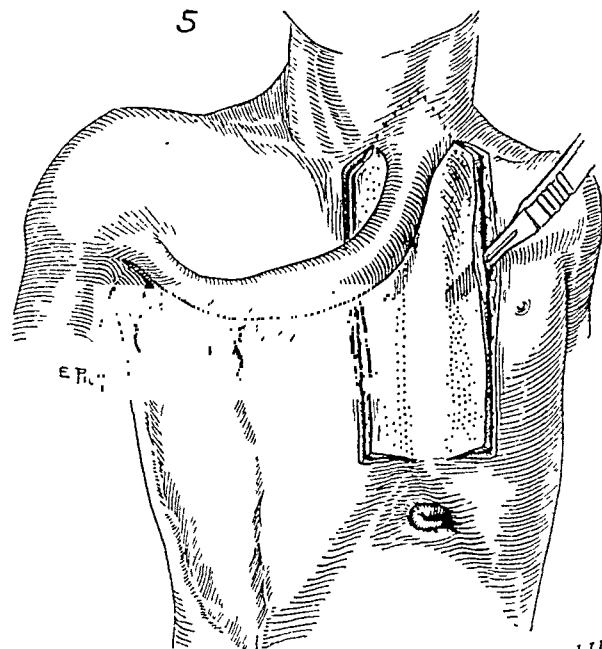


FIGURE 10. Fifth Step of the Operation for Types III and IV.
5 shows the incision for making the epithelial-lined tube.

edges together with the skin inside. The raw surface is then covered by undermining the skin on either side of the skin tube and bringing these flaps over the skin tube. The objection to this plan is the requirement of tension sutures, which are undesirable, and the fact that the newly constructed skin esophagus must necessarily be compressed, making it difficult for food to pass through it. To obviate these disadvantages, other surgeons have covered

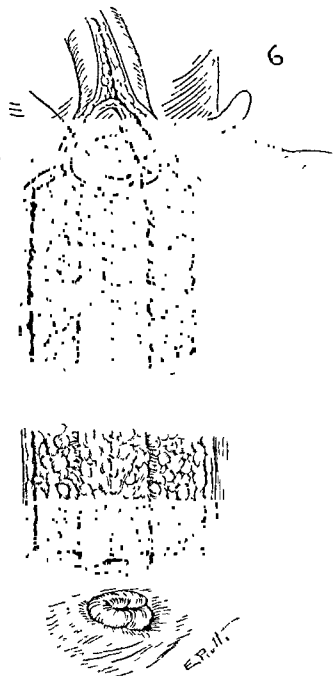


FIGURE 11. Fifth Step of the Operation for Types III and IV. It shows the construction of the epithelial-lined tube, which is covered by the tube graft, as shown in Figure 12.

the raw surface of the skin tube with a free graft. Although this has proved satisfactory in adults, it was the disadvantage in infants of requiring pressure while the graft is taking, and it also leaves a thin-walled tube, which is subject to leakage or injury. To avoid these objections, the following plan was adopted. First, a tube graft of appropriate length is raised on the right side of the chest, starting in the right axilla and running down onto the abdominal wall in front of the iliac crest. The raw surface under this tube is covered by a Thiersch graft to avoid pulling over the skin of the chest wall (Fig. 8). Some three weeks later the lower end of this tube graft is freed and sutured to the skin

of the neck over the esophageal opening, as shown in Figure 9. After this tube graft has acquired its

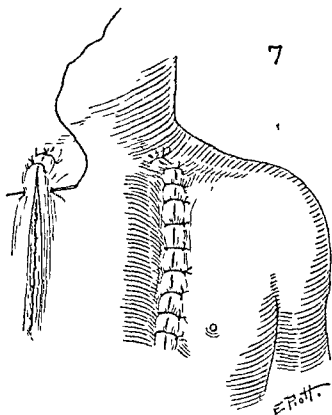


FIGURE 12. Fifth Step of the Operation for Types III and IV. It shows the tube graft being placed over the epithelial-lined tube and being sutured in place.

new circulation from the neck, the epithelial-lined tube that is to act as an esophagus is constructed and covered by the tube graft, as shown in Figures

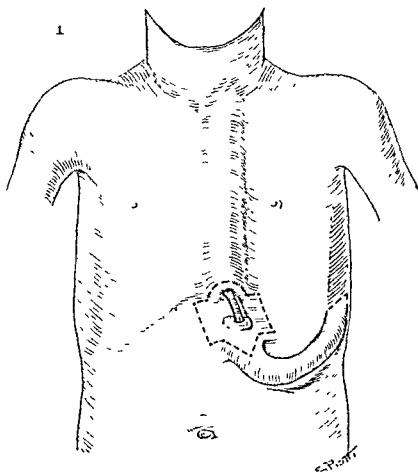


FIGURE 13. Final Step of the Operation for Types III and IV. It shows the second tube graft, which is to be used for the covering of the lower part of the epithelial-lined tube.

10, 11, and 12. These procedures leave an epithelial-lined tube with a good skin covering carried to within a few centimeters of the gastrostomy opening (Fig. 13).

The next step is similar to what was carried out with the upper skin tube. A small tube graft is raised in the left flank with its end transferred to a position just below the gastro-

tomy opening. An inverted skin tube is constructed to include the gastrostomy opening and to connect with the upper skin tube, as shown in Figure 1. The tube graft is used to cover the raw surface

TABLE 4. Cases of Esophageal Atresia with or without Tracheoesophageal Fistula Operated on at the Children's Hospital, 1940-1944.

HOSP. NUMBER	DATE OF ADMISSION	AGE AT ADMISSION	SEX	TYPE	OPERATION	OPERATOR	DURATION OF LIFE
240342	11/28/39 3/15/40	1 day 4 mo.	F	III	Gastrostomy Ligation of tracheoesophageal fistula Exteriorization of cervical esophagus Anterior thoracic esophagus	Dr. Ladd	Living (4 3/12 yr.)
249209	2/ 4/41	3 days	M	III	Ligation of tracheoesophageal fistula Gastrostomy	Dr. Gross	6 days
249410	2/10/41	2 days	M	III	Ligation of tracheoesophageal fistula	Dr. Ladd	3 days
251743	5/ 7/41	18 hr.	M	III	Ligation of tracheoesophageal fistula	Dr. Lanman	2 days
256430	10/13/41	2 days	M	IV	Primary anastomosis to esophagus Gastrostomy	Dr. Gross	30 days
257773	12/ 2/41	5 days	F	I	Gastrostomy Marsupialization of esophagus	Dr. Ladd	36 days
257275	12/15/41	2 days	M	I	Gastrostomy Marsupialization of esophagus	Dr. Ladd	Living (2 3/12 yr)
257185	12/18/41	1 day	F	IV	Ligation of tracheoesophageal fistula Gastrostomy Marsupialization of esophagus	Dr. Ladd	6 days
258624	12/30/41	1 day	M	IV	Ligation of tracheoesophageal fistula Gastrostomy	Dr. Ladd	5 days
258658	1/ 9/42	2 days	F	IV	Ligation of tracheoesophageal fistula	Dr. Gross	3 days
259379	3/ 1/42	8 days	M	III	Ligation of tracheoesophageal fistula	Dr. Gross	11 days
261528	5/16/42	2 days	F	V	Ligation of tracheoesophageal fistula Gastrostomy	Dr. Ladd	8 days
265092	9/8/42	3 days	M	III	Ligation of tracheoesophageal fistula Gastrostomy and marsupialization of esophagus	Dr. Ladd	35 days
266051	9/27/42	2 days	M	III	Ligation of tracheoesophageal fistula Gastrostomy and marsupialization of esophagus	Dr. Ladd	106 days
267150	10/16/42	1 day	F	III	Anastomosis of esophagus and ligation of tracheoesophageal fistula	Dr. Gross	1 day
267162	10/19/42	4 days	M	III	Ligation of tracheoesophageal fistula Gastrostomy and marsupialization of esophagus Secondary ligation of tracheoesophageal fistula	Dr. Ladd	Living (17 mo)
268156	11/25/42	5 days	M	IV	Anterior thoracic esophagus Ligation of tracheoesophageal fistula Gastrostomy and marsupialization of esophagus	Dr. Ladd	147 days
268827	12/15/42	4 days	M	III	Ligation of tracheoesophageal fistula	Dr. Ladd	7 days
268997	2/14/43	4 days	F	III	Ligation of tracheoesophageal fistula	Dr. Gross	6 days
271085	3/30/43	3 days	M	III	Ligation of tracheoesophageal fistula with direct anastomosis	Dr. Ladd	6 days
272514	4/29/43	4 days	M	III	Ligation of tracheoesophageal fistula	Dr. Ladd	6 days
274245	7/14/43	7 days	M	III	Marsupialization of esophagus	Dr. Ladd	10 days
275005	7/20/43	3 days	F	III	Ligation of tracheoesophageal fistula Partial excision of duplication of stomach and gastrostomy Marsupialization of esophagus	Dr. Ladd	10 days
275631	8/10/43	6 days	F	III	Ligation of tracheoesophageal fistula with primary end-to-end anastomosis Gastrostomy	Dr. Ladd	Living (7 1/4 mo)
275095	8/23/43	4 days	F	III	Ligation of tracheoesophageal fistula Gastrostomy Marsupialization of esophagus	Dr. Ladd	Living (7 mo)
276726	9/18/43	3 days	M	III	Ligation of tracheoesophageal fistula	Dr. Ladd	8 days
277394	9/22/43	15 days	M	III	Ligation of tracheoesophageal fistula with primary esophageal anastomosis	Dr. Gross	17 days
277277	9/27/43	4 days	M	III	Ligation of tracheoesophageal fistula Gastrostomy Marsupialization of esophagus	Dr. Ladd	Living (6 mo)
276847	10/ 7/43	6 days	F	III	Esophageal anastomosis with ligation of tracheoesophageal fistula	Dr. Ladd	9 days
276848	10/ 8/43	5 days	M	III	Ligation of tracheoesophageal fistula Gastrostomy	Dr. Ladd	Living (5 1/2 mo)
278319	10/23/43	10 days	M	III	Primary anastomosis of esophagus with ligation of tracheoesophageal fistula Gastrostomy	Dr. Gross	Living (5 mo)
278540	11/20/43	2 days	M	IV	Ligation of tracheoesophageal fistula Gastrostomy Marsupialization of esophagus	Dr. Ladd	Living (3 1/4 mo)
279539	12/30/43	3 days	F	IV	Ligation of tracheoesophageal fistula Marsupialization of esophagus	Dr. Ladd	Living (2 1/4 mo)
280539	2/ 9/44	2 days	F	I	Mediastinal exploration Gastrostomy Marsupialization of esophagus	Dr. Ladd	Living (1 1/4 mo)

small tube graft is raised in the left flank with its end transferred to a position just below the gastro-

with the upper skin tube, as shown in Figure 1. The tube graft is used to cover the raw surface

is previously done above. Figure 15 shows the anterior thoracic esophagus completed in the oldest patient, who is now over four years of age.

Since 1939 we have operated on 34 patients according to our present method (Table 4). Of these patients, 6 have had primary anastomosis of the esophagus and 2 are living. Twenty-eight patients

patient, who also had a Type IV lesion, died a week after the operation with pneumonia as the main cause of death, but this infant also had a congenital heart lesion. A third patient, whose malformation was of Type I, died a month after the operation. There was considerable technical difficulty with the gastrostomy on account of the extremely small size

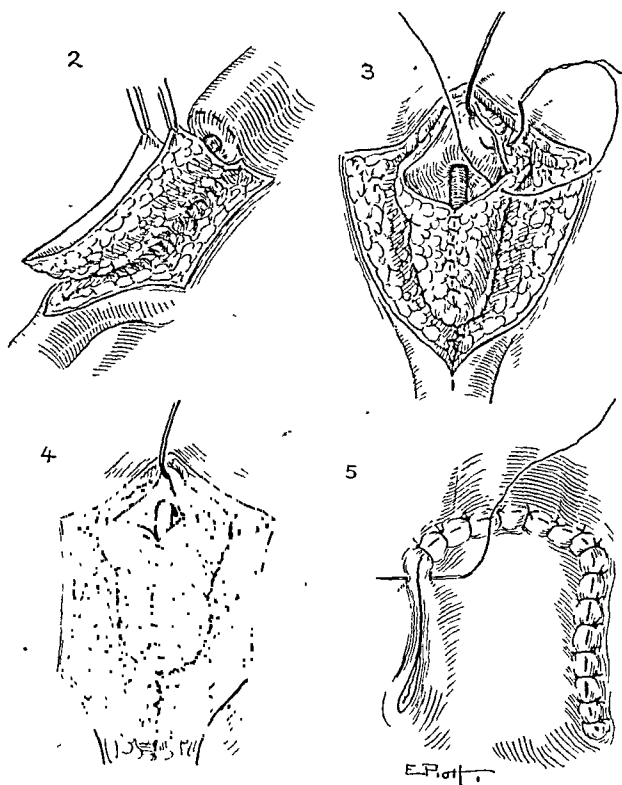


FIGURE 14. Final Step of the Operation for Types III and IV.

2 shows the flaps being elevated to form the epithelial-lined tube; 3 and 4 show their being sutured to the previously made epithelial-lined tube; and 5 shows the raw surface's being covered by the tube graft and being sutured.

have had the three-stage operation consisting of obliteration of the esophageal fistula and gastrostomy and esophagostomy; 9 of these patients are living.

A few examples of the causes of death in the patients not living are of interest. The cause of one death appeared to be the usual pneumonia, the effects of the operation and, as a contributing factor, an open intraventricular septum and other cardiac anomalies. This was a Type IV anomaly. A second

of the stomach. The blind end of the lower segment of the esophagus was a little over a centimeter above the diaphragm, making a primary anastomosis of the esophagus out of the question. In a fourth case, one of Type IV, death occurred on the fifth postoperative day with pneumonia as the main cause. In a fifth case, of Type V, the patient died on the fifth day of life. Death was due to pneumonia and failure to recognize a fistula extending from the upper esophageal segment to the trachea,

A sixth patient, with a Type IV anomaly, did extremely well for a month after the tracheoesophageal fistula was tied off, the upper segment of the esophagus had been marsupialized and a gastrostomy had been performed. He gained in weight steadily and

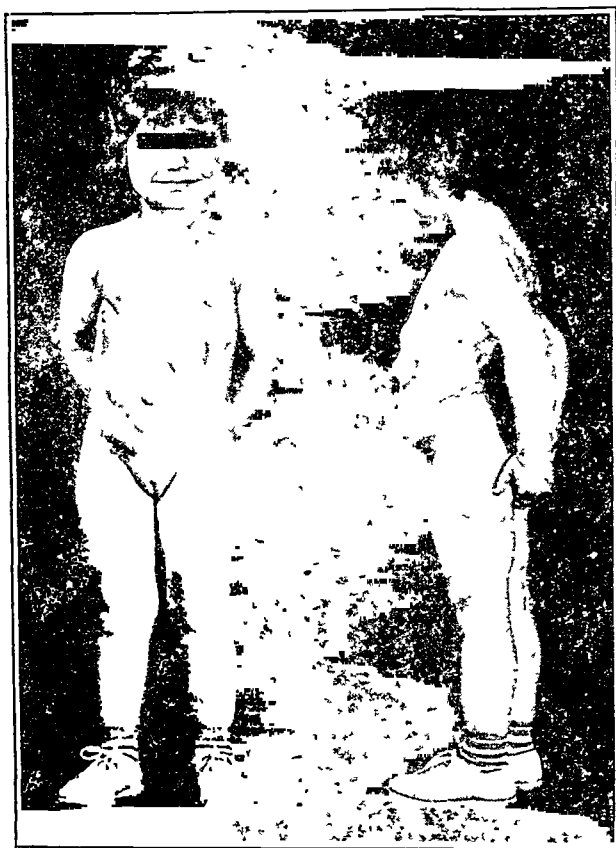


FIGURE 15 *Functioning Anterior Thoracic Esophagus in a Child Four Years Old Who Takes a Liberal Diet.*

was in excellent condition, but died suddenly of asphyxia that at post-mortem examination was found to be due to regurgitation of fluid fed through a recanalized tracheoesophageal fistula. The death of a seventh patient (Type IV) was most disappointing. This patient had done extremely well for three months and a half, when he became infected by an epidemic enteritis from which he died within twenty-four hours of its onset.

Of the 11 living patients, the oldest is now over four years of age. She eats a moderately varied diet and indulges in fairly normal activities for a child of her age. Her only complaint consists of occasional attacks of pain in the lower end of the new esophagus, apparently due to contraction of the gastrostomy opening, which requires dilatation. The next oldest patient is a little over two. The anterior thoracic esophagus has been completed, but there is a pin-sized leak that is slow in healing. The third oldest patient is seventeen months old, is in excellent health and is in the process of having his anterior thoracic esophagus constructed. The other 6 patients, who have been operated on by the

three-stage method with the anticipation of constructing an anterior thoracic esophagus, are seven months, five and three-quarter months, five and a half months, three and three-quarter months, two and a half months and one and a quarter months old, respectively. They are all doing well and gaining in weight regularly. It is worthy of note that the last two patients were born a few weeks prematurely weighing 4 pounds, 6 ounces, and 4 pounds, 10 ounces, respectively.

Of the 2 living patients on whom a direct anastomosis was done, one is a little over seven months old and the other is five months old. The older of these is being fed entirely by mouth, is gaining in weight and is doing well. The younger patient is still being fed partially by mouth and partially



FIGURE 16 *Seven-Month-Old Baby with a Direct Anastomosis. All feeding is done by mouth, and the infant weighs over 15 pounds.*

by gastrostomy. He has had some respiratory difficulty, but this is improving and he is gaining in weight (Fig. 16).

SUMMARY

From our experience and that of others, it seems fair to conclude that atresia of the esophagus with or without tracheoesophageal fistula should no longer be considered as a hopeless condition carrying with it a 100 per cent mortality. It also seems justifiable to predict that if obstetricians and pedi-

atricsians are on the alert for making an early diagnosis, the mortality will be further lowered.

It should also be stated that the surgical methods for combating this condition are subject to change. At the present time, however, primary anastomosis of the esophagus appears to be the operation of choice when the two ends of the esophagus can be approximated without too much tension. In other cases, where the ends of the esophagus are far apart, the three-stage operation with the ultimate construction of an anterior thoracic esophagus is a safer operation. The last 5 patients operated on according to this plan are living and doing well.

I am indebted to Dr. Sidney Farber for his careful post-mortem observations, and to Dr. Taguc C. Chisholm for reviewing the literature and tabulating the statistics.

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HEREDITARY HEMORRHAGIC TELANGIECTASIA*

An Analysis of Capillary Heredopathies

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WALTHAM, MASSACHUSETTS

THE hereditary hemorrhagic diatheses constitute an interesting group of relatively rare conditions that, in general, may be considered to fall into three main groups. The first group includes conditions characterized by hereditary disturbances in the plasma components of the hemostatic mechanism, and is exemplified by hereditary hypofibrinogenemia and probably hemophilia. In the second group are placed those hereditary conditions showing alteration in the platelets. This alteration may be a quantitative diminution (hereditary thrombocytopenic purpura) or a qualitative change in platelet function (thrombasthenia). The third group comprises the hereditary disorders of capillary structure and functions — the capillary heredopathies. They are transmitted by, and appear in, both sexes. All hitherto described capillary heredopathies present a normal platelet count and normal clotting and prothrombin times. The usual classification of these disorders is in terms of the results obtained by various functional tests, such as the bleeding time and the tourniquet test. Three capillary heredopathies are ordinarily considered well-defined entities; these are pseudohemophilia, hereditary familial purpura and hereditary hemorrhagic telangiectasia.

Pseudohemophilia (Glanzmann,¹ Morawitz, and Jürgens² and von Willebrand and Jürgens³) is characterized by an increased bleeding time. The tourniquet test may be positive or negative, and it is claimed that in some cases clot retraction is defective. The latter findings, however, vary not from case to case but from family to family. Epistaxis, spontaneous ecchymoses, prolonged bleeding after operation, spontaneous bleeding from mucous membranes and an onset in early life with decreasing severity in later life are the usual clinical manifestations.

Hereditary familial purpura simplex (Davis⁴) is characterized by the appearance of spontaneous ecchymoses and a positive tourniquet test but a normal bleeding time. Further clinical observations included a low incidence of other forms of spontaneous bleeding and frequent association with rheumatoid arthritis and rheumatic fever. A family described by Davis⁴ had hereditary hemorrhagic telangiectasia as well as hereditary familial vascular purpura.

Hereditary hemorrhagic telangiectasia (Rendu,⁵ Osler^{7,8} and Weber⁹) is the third of the well-demarcated capillary syndromes. It is characterized by a normal bleeding time and typical gross disseminated capillary abnormalities. A negative tourniquet test is usually included as a diagnostic criterion. The characteristic angiomas are composed of

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dilated small vessels that histologically comprise a single layer of endothelium with a conspicuous deficiency of the muscular and elastic layers of the vessel wall.¹⁰⁻¹² Clinically, bleeding, particularly epistaxis, usually begins at about the second decade of life. Visible telangiectases, which in most cases bleed with minimal trauma, appear somewhat later. Telangiectases are most frequently found in the nose and mouth and on the face, neck and hands. All other organs, including the viscera, may be involved. In one family not only a tendency to telangiectasia but also a monosymptomatic location in the lung was inherited.¹³ Severe cases are associated with hypochromic microcytic anemia, splenomegaly and, more rarely, hepatomegaly.

Any attempt to classify hereditary hemorrhagic disorders in general, and capillary heredopathies in particular, encounters certain difficulties. These are partly due to uncertainties in the interpretation of the mechanism of the various tests on which separation of these syndromes is based, and partly due to coexisting combinations of various types in the same family (Fig. 1).¹⁴ For example, it has been noted that some pseudohemophilic families show a positive tourniquet test as well as a prolonged bleeding time, whereas others show only a prolonged bleeding time. Some families are said to have deficient clot retraction, whereas in others the clot retraction is normal. Furthermore, combinations of thrombocytopenia with capillary disorders may be seen.¹⁵

This paper describes a family in which the typical lesions of hereditary hemorrhagic telangiectasia, together with a positive tourniquet test, were present in all members examined.* Since the presentation of rare and unusual syndromes is chiefly of value for the light that it throws on general pathologic physiology, an attempt is made to discuss the underlying mechanisms of the capillary heredopathies.

CASE REPORTS

CASE 1. R. Z., an 80-year-old woman, came under observation because of repeated spontaneous epistaxis over a period of 40 years. Cauterization of the nose 7 years previously had afforded relief for only 6 months. For 30 years she had noted red spots on the ends of the fingers and on the mucous membranes of the mouth. There were no spontaneous ecchymoses, nor was there increased bleeding after minor injury. Before the menopause, which occurred at the age of 45, the menses had not been unusual except for slight hypermenorrhea. A careful investigation of the nutritional background revealed a diet that was qualitatively and quantitatively adequate. There had been occasional attacks of migraine at the menstrual period; these ceased at the menopause. The history was otherwise noncontributory, except for some episodes of acute arthritis 20 years previously.

Physical examination revealed a well-developed, well-nourished woman who looked and acted much younger than her age. On the roof of the mouth, the frenulum of the tongue, the palm, the fingers and to a lesser extent the forearm were found the typical lesions of telangiectasia. The mouth and teeth were in excellent condition. Except for Heberden nodes on the fingers, no pertinent physical findings were noted.

While the patient was under observation the temperature varied from 97.0 to 98.6°F., and the pulse from 70 to 80.

*We are indebted to Drs. James Burns and Ralph Manning for permission to report these cases.

Several blood-pressure determinations ranged closely about 140/60. Repeated urinalyses were negative.

The red-cell count was 4,100,000, with 3 per cent reticulocytes, and the hemoglobin was 14 gm. (90 per cent). The white-cell count was 9100, with 5 per cent staff cells, 67 per cent neutrophils, 21 per cent lymphocytes, 4 per cent monocytes and 3 per cent eosinophils. The color index was 1.08. The hematocrit was 38 and the mean corpuscular volume 92 cubic microns. The platelet count was 220,000 (Rees-Ecker method). Clot retraction was normal. The prothrombin time was 20 seconds (normal, 18 seconds) (Quick method). The bleeding time was 2 minutes (Duke method), the clotting time 4 minutes (Lee-White method) and the sedimentation rate 9 mm. in 1 hour (Wintrobe method).

A tourniquet test was performed by placing a blood-pressure cuff on the upper arm and inflating it to halfway between the systolic and the diastolic pressure. After 15

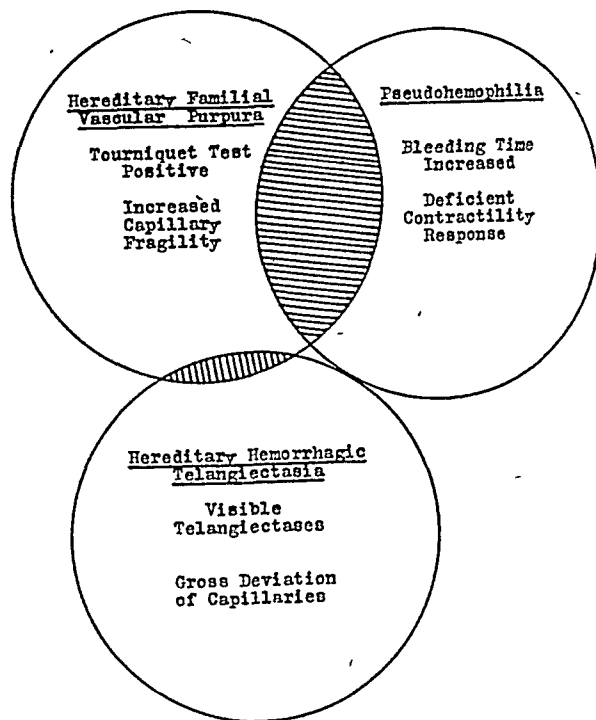


FIGURE 1. Diagram Illustrating the Various Pure Types and the Reported Combinations of Hereditary Capillary Syndromes. The shaded areas represent the observed combinations and their respective frequencies. An association of increased bleeding time (pseudohemophilia) and gross deviation of capillaries (telangiectasia) has not yet been reported.

minutes, the number of petechiae were counted in a circle 2.5 cm. in diameter that had been drawn on the flexor surface of the forearm 4 cm. below the bend of the elbow. No petechiae were found in this area before beginning the test, and 60 to 70 were found after testing; the test was therefore distinctly positive, since 10 petechiae are considered to be the upper limit of normal.¹⁶

Further investigation revealed a strong familial and hereditary tendency to telangiectasia (Fig. 2). The patient's father had had marked telangiectasia and epistaxis, which was occasionally severe enough to lead to fainting. Because the patient left home at an early age, no information about her father's further history was available, nor could information about earlier generations be secured. There were two sons, the younger of whom died of diphtheria at the age of 2. The elder was asymptomatic until the age of 22, when epistaxis commenced. It is interesting to note that he had been able to play

the trombone until this time but was then forced to stop because it induced epistaxis. Typical telangiectases developed later, but bleeding never became so severe as that of the mother. This son died at 55 of peritonitis.

There are reports on 66 members of the family (33 males and 33 females), 16 of whom (8 boys and 8 girls) have telangiectasia (a certain number are too young to show lesions as yet). The sex incidence, therefore, is not remarkable.

Certain other interesting details were encountered. In one line, telangiectasia was present in the first generation but not in the second or third, and reappeared in the fourth generation. This so-called

In comparing Case 2 with Case 1, it was noted that the tendency to bleed from the visible telangiectases and the tendency to easy bruising were more marked in the former. Epistaxis was more marked and the tourniquet test was somewhat more strongly positive in the latter. In Case 3 (below) similar findings were present, but the tendency to easy bruising was even more prominent and the tourniquet test was the most strongly positive of the 3 cases.

CASE 3. C. M., a 46-year-old housewife, reported repeated spontaneous epistaxis beginning at the age of 8. Telangiectases on the hands were first noticed at 20, and increased in number with increasing age. The patient bruises

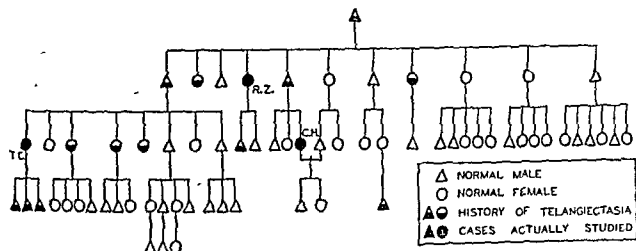


FIGURE 2. The Family Tree.

"skipping" has been described by Fitzugh.¹⁷ One instance of intermarriage within the family was noted. In this case, a girl of the third generation with telangiectasia married her first cousin, of the third generation, who did not have telangiectasia. There were two children—a hypernatremic stillbirth and an infant with complete spina bifida. The association of hereditary hemorrhagic telangiectasia with anomalies of the vertebral column has previously been reported.¹⁸⁻²⁰

Unfortunately, this family had become spread throughout the United States and only 2 other members (Cases 2 and 3) could be examined.

CASE 2. T. C., a 49-year-old, married woman has had repeated spontaneous epistaxis since the age of 11. Telangiectatic lesions appeared on the hands in the 30th year, and much more extensive distribution developed at the menopause. There have been no spontaneous ecchymoses or increased bleeding after small injuries, but the patient bruises easily. At the age of 37 she had "arthritis," which was relieved after tooth extraction, and she had hay fever, asthma and urticaria. The menses were regular and were not remarkable except for some hypermenorrhea. The menopause occurred at the age of 45.

Physical examination revealed the typical lesions of hereditary telangiectasia on the face and hands and in the mouth. Telangiectasis was also found under the nail of the left 5th toe. The physical findings were otherwise noncontributory.

The red-cell count was 5,280,000, and the hemoglobin was 15.3 (93 per cent), giving a color index of 0.9. The white-cell count was 7500, with a normal differential pattern. The platelet count was 250,000. The bleeding time was 2½ minutes, and the clotting time 4 minutes. A tourniquet test was distinctly positive.

A number of siblings have migraine and the patient herself had epistaxis in early adulthood. Her 3 children have epistaxis. The youngest son, aged 25, has already developed telangiectasia on the hands.

easily. She occasionally bleeds from telangiectases on the tongue and lips. The menses are regular, but there is marked hypermenorrhea.

The patient married her first cousin, who, although in the direct line of descent, was not afflicted with telangiectasia. There were three pregnancies. One was terminated by spontaneous miscarriage, one child of 13 pounds was stillborn, and the other lived only 3 days after birth. The description of one of these children is compatible with complete spina bifida.

Physical examination revealed a well-developed, well-nourished woman who presented the typical lesions of hereditary telangiectasia on the hands, tongue, lips, face and the mucous membranes of the buccal cavity. No other significant physical findings were elicited.

The red-cell count was 4,600,000, the hemoglobin 14.3 gm. (92 per cent), the color index being 1.0. The white-cell count was 7800, with a normal differential pattern. The platelet count was 325,000. The bleeding time was 2 minutes, and the clotting time 3½ minutes. A tourniquet test was strongly positive.

DISCUSSION

Occurrence of Positive Tourniquet Tests in Hereditary Telangiectasia

The outstanding peculiarity of this family is the occurrence of a positive tourniquet test in a syndrome in which a negative tourniquet test is ordinarily considered a diagnostic criterion. For example, the tables given for the differential diagnosis of the hereditary hemorrhagic diatheses in current textbooks of hematology²¹⁻²³ include this as an important item. Although only 3 members of the family could be examined, the occurrence of the unusual combination of a positive tourniquet test with telangiectasia in all of them makes it likely that both abnormal capillary manifestations were present on a hereditary basis.

A review of the literature on hereditary hemorrhagic telangiectasia of the last ten years shows that most of the authors reporting cases^{12, 24-31} do not mention having performed a tourniquet test or suction test. Five authors^{10, 18, 32-34} report performing tourniquet tests in 9 cases. The result was negative in 8 cases and questionable in 1.

The only report of an unequivocally positive tourniquet test that can be found is that of Davis,^{4, 5} who in his study of hereditary familial purpura simplex reports a family with spontaneous ecchymoses, a positive tourniquet test and typical lesions of hereditary hemorrhagic telangiectasia. These findings are similar to those in our family, except that our patients do not show spontaneous purpuric lesions.

Whether the association of a positive tourniquet test with hereditary telangiectasia is fortuitous or is indicative of a more fundamental capillary disturbance presents a problem that necessitates a brief analysis of the clinical pathology of capillary heredopathies.

Clinical Pathology of Capillary Heredopathies

In considering capillary functions it is important to distinguish three variables: the contraction of the capillaries following injury (contractility response), the resistance of the capillaries to pressure (capillary fragility) and gross deviation in the histologic structure of the capillaries (telangiectasia). It will be seen that although disturbances of these factors most often occur separately, defects frequently coexist.

Contractility response of capillaries following injury. Following an injury to the capillaries, bleeding stops because of a complicated process involving contraction of the capillaries and plugging of the endothelial defect by a platelet thrombus. MacFarlane,³⁵ to whom much of the credit for the modern concepts in this field must be given, believes that the capillary contraction is the more important process. Prolonged bleeding following capillary injury may therefore be due to diminished contractility, or to quantitative or perhaps qualitative alteration of the platelets, or to a combination of these factors.

Clinically, a prolonged bleeding time is seen in such conditions as thrombocytopenic purpura of various etiologies and in conditions with apparently normal platelets but an abnormal contractility response. In pseudohemophilia, the platelet counts are normal, but deficient capillary contractility has been demonstrated by MacFarlane. The earlier concept of pseudohemophilia, as developed by von Willebrand and Jürgens,³ Morawitz and Jürgens² and others, favored a qualitative alteration of platelets with diminished ability to form a thrombus. Serious doubt has been cast on the validity of this concept. Buckman,³⁶ for example, found that a suspension of platelets obtained from a pseudohemophilic patient produced as rapid a coagulation

of hemophilic blood as did the platelets from a healthy person. At present, although the possibility of qualitative platelet alterations is still undecided, the capillary dysfunction in pseudohemophilia is well established. That diminution of platelets alone does not lead to purpura unless accompanied by capillary damage has been experimentally demonstrated. Roskam³⁷ injected gelatin intravenously into dogs and reduced the platelets to extremely low levels with only a slight or no increase in bleeding time. Bedson,¹⁴ using a solution of agar, obtained similar results. If, however, injections of antired-cell serum preceded the lowering of the platelets, purpura resulted. Antired-cell serum, according to Bedson, damages the capillaries.

Prolonged bleeding time in the presence of apparently normal platelets—as indicated by a normal platelet count and coagulation time—is therefore indicative of a deficiency in capillary contractility response. Furthermore, a deficient contractility response may appear only in localized areas. Roskam³⁷ reported a case in which the patient had a bleeding time of three minutes in one ear lobe and one of forty-eight minutes in the other. It is not improbable that some of the cases of hereditary familial epistaxis without other detectable hematologic deviation¹⁵ represent such localized areas of defective contractility response.

Response of capillaries to pressure. The capillary fragility expresses the resistance of the capillaries to pressure. This is best measured by a modern tourniquet test or by the more elaborate suction method.^{16, 38, 39} These fragility tests depend on the integrity of the capillary endothelium. Clinical observations suggest some relation between platelets and maintenance of the capillary resistance to pressure. In the presence of a normal platelet count and coagulation time, however, a positive tourniquet test may be considered to reflect only an abnormal response of the capillaries to pressure.

Increased capillary fragility may be present with or without corresponding involvement of the contractility response. Since capillary fragility is measured by the tourniquet test, a prolonged bleeding time may therefore be seen with or without a positive tourniquet test, and similarly a positive tourniquet test may be seen independently of an increased bleeding time. A decrease in capillary resistance without a disturbance in contractility response was described by Davis^{4, 5} as hereditary familial vascular purpura. A disturbance in contractility response without a change in capillary resistance is seen in certain pseudohemophilic families.

As yet, localized disturbances of capillary resistance have not been described, probably because the tourniquet test, which has been most widely used for testing capillary resistance, is ordinarily performed only on the upper extremities. With the

introduction of suction tests, however, it will become possible to study localized variations. Analysis of capillary contractility response and fragility, together with their occurrence in clinical observations, have therefore shown that they must be considered as independent variables.

Gross deviation of structure of capillaries. Areas of gross deviation of capillary histologic structure are seen in hereditary hemorrhagic telangiectasia as localized, disseminated lesions. The gross pathology and histopathology have already been described.

The usual form of gross deviation, or typical hereditary hemorrhagic telangiectasia, occurs as multiple lesions in various capillary provinces, but localized single lesions of hereditary telangiectasia are sometimes seen. Libman and Ottenberg¹¹ described a family in which a single lesion in the lung occurred as a familial characteristic.

As a rule, the nonaffected areas in this disease show a normal contractility response and fragility, whereas bleeding time after injury to a telangiectasis is considerably prolonged.²² In certain cases, however, gross deviation of the capillaries is combined with more or less developed abnormalities of contractility response or capillary fragility, precisely as defects in contractility response and fragility are associated. Our family and that reported by Davis^{4,5} show such a combination of hereditary hemorrhagic telangiectasia with abnormal capillary fragility. The sole difference is that Davis's family showed spontaneous ecchymoses, whereas the increased fragility in our cases was not sufficient to lead to purpuric manifestations. The combination of hereditary hemorrhagic telangiectasia with prolonged bleeding time (deficient contractility response) has not yet been reported, but on the basis of this analysis it may be considered possible.

As can be seen from this discussion, definite pure types of capillary dysfunction are sometimes observed. On the other hand, the diagnosis of a clinical picture in any case of hereditary capillary disorder should depend on analysis of the involved pathologic physiology. Such analysis shows the existence of an interrelated system of capillary functions that may be singly or simultaneously involved. This approach precludes the use of tables of differential diagnosis for these disorders in which only rigidly demarcated types are considered. In the various manifestations of acquired capillary dysfunctions, toxins, nutritional deficiencies (vitamin P deficiency), endocrinopathies and so forth play a role as etiologic factors. No clue is available concerning the mechanism by which the hereditary manifestations are brought about.

SUMMARY

A family presenting hereditary hemorrhagic telangiectasia, together with a positive tourniquet

test, is described. An analysis of the pathologic physiology of capillary hereditary disorders is attempted. An abnormal contractility response of a capillary to injury as expressed by a prolonged bleeding time and an abnormal capillary fragility to pressure, as seen by a positive tourniquet test, represent independent variables that may be singly or simultaneously involved.

Pseudohemophilia is characterized by a prolonged bleeding time but a negative tourniquet test, and hereditary purpura simplex by a normal bleeding time but a positive tourniquet test. Combinations of both types exist.

Hereditary hemorrhagic telangiectasia is a localized gross abnormality of capillaries usually not accompanied by any systemic capillary dysfunction. The observed family represents, however, such a combination of localized gross deviation of capillary structure and increased capillary fragility.

The diagnosis of hereditary capillary syndromes should depend on physiologic analysis and not on rigidly demarcated types of disorders.

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MEDICAL PROGRESS

ENDOSCOPY*

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SOMETIMES wonder whether the general practitioner thinks that the endoscopist, peeking through narrow tubes, is "learning more and more about less and less," but when I come to review the voluminous literature on the subject, I realize each year more than ever how many interesting branches of medicine and surgery are involved. Undoubtedly the endoscopist sees a large percentage of the most interesting problem cases in the hospital. Through bronchoscopy and esophagoscopy he is constantly in touch with the new and ever-widening field of thoracic surgery. When he uses the gastroscope, he is endeavoring to confirm or establish gastric diagnoses that might otherwise be obscure or unattainable. Last, but not least, by the use of the peritoneoscope he is differentiating many difficult abdominal problems and establishing a positive diagnosis by biopsy. A review of the literature may help the clinician in deciding when to call the endoscopist in consultation.

ANESTHESIA

There have been a number of verbal reports regarding the toxicity of pontocaine as a topical anesthetic during endoscopy. In last year's progress report¹ a nonfatal reaction was reported. Hansen and Stealy² report a sudden death following the use of pontocaine as a gargle anesthetic. The patient was a man of fifty-four who had received 1½ gr. of pentobarbital sodium orally one hour before, and ¼ gr. of morphine sulfate fifteen minutes before the operation. While gargling 1 dram of 2 per cent pontocaine, he suddenly collapsed. Respiration ceased, cyanosis developed and there was a general-

ized convulsion, followed by several more convulsions during the next hour. In spite of artificial respiration and the administration of luminal sodium, adrenalin, coramine and oxygen, death ensued one hour and a quarter after the collapse. A post-mortem examination revealed a carcinoma of the esophagus with extensive metastases to the liver, but no organic reason for the sudden death could be demonstrated. Because of the manner in which death occurred, and the absence of any other demonstrable cause, it can be concluded only that death was due to an anaphylactic reaction to the pontocaine gargle.

In the clinic at the Massachusetts General Hospital a 4 per cent cocaine for all peroral endoscopies is being used. No reaction to 5 per cent Larocaine Hydrochloride has been known to occur but at the present time this drug cannot be obtained.

In an editorial on modern anesthesia, Lahey³ states that the anesthetist should recognize the importance of keeping the tracheobronchial tree free of secretions and other fluid, and should be prepared and able to remove these secretions before, during and after operation; in other words, he should be familiar with the technic of bronchoscopy and should be able to recognize when this procedure is indicated.

BRONCHOSCOPY

Anatomy. Jackson and Huber⁴ have studied the anatomy of the bronchial tree and lungs with reference to the branching into lobar segmental bronchi and the relation of each lobar and segmental bronchus to its corresponding portion of lung. A nomenclature has been proposed that is quite similar to that suggested by Adams and Davenport.⁵

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Diverticulum of the bronchus. Diverticulum of the bronchus is exceedingly rare. Arce⁶ reports an interesting case that was well demonstrated by bronchography.

Bronchiectasis. Goodale⁷ reports 75 cases of bronchiectasis that were studied to evaluate the importance of surgical treatment of the sinuses. The best results were obtained from lobectomy in cases in which there was no complicating sinusitis. Untreated sinusitis was a distinct hindrance to recovery from the thoracic infection. Likewise, in cases in which the sinuses were operated on but lobectomy was not done, the result was poor. When both adequate operation on the sinuses and lobectomy can be performed, the results are so much better that these two procedures are indicated in all suitable cases. That Goodale's cases were hard to classify may be considered evidence that each patient must be considered separately.

In reporting on 76 patients surgically treated for bronchiectasis, Bradshaw and O'Neill⁸ mention that more and more patients with bilateral disease are being subjected to bilateral lobectomy, with considerable success (Eloesser, Lewis, Overholt, Bradshaw and Chodoff, Blades and Graham). Several patients have had three and a part of a fourth lobe removed successfully. The operative mortality in this group of patients is, of course, much higher than that in the unilobar group.

DeBaKey and Ochsner⁹ have also written on the surgical treatment of bronchiectasis, calling particular attention to Churchill's¹⁰ recently reported series of 125 cases in which lobectomy was performed with a mortality of only 2.4 per cent. The operative mortality is lowest with children and increases with age. The authors use bronchoscopic aspiration following the operation. The decreased postoperative morbidity resulting from the removal of viscid mucopurulent secretions by this means has convincingly demonstrated its value.

Blades and Dugan¹¹ have demonstrated that, following atypical pneumonia, iodized oil bronchograms occasionally give the erroneous impression of a true bronchiectasis. According to them, if one is aware that atypical pneumonia is capable of producing temporary dilatation of the bronchi, an early or dry bronchiectasis can for a time be considered a pseudobronchiectasis. Progression of symptoms and repeated demonstration of the bronchial dilatation soon establish the correct diagnosis. Failure to consider the possibility of pseudobronchiectasis may result in unnecessary resection of lung tissue.

Vinson,¹² in a discussion of the management of chronic suppurative pulmonary disease, states his belief that any patient with suppuration should have at least one bronchoscopic examination to determine the exact location and distribution of the area of infection. When bronchial stricture is present, adequate drainage can be often provided by bronchoscopic methods, with beneficial or cura-

tive results. Insufflation of powdered sulfanilamide through the bronchus has been of benefit in patients with chronic suppuration. My own experience indicates that sulfadiazine by mouth is equally effective.

Clerf¹³ believes that although bronchiectasis can be cured by conservative measures, this can be considered only if the cases are observed early, before the bronchial mucosa or bronchial wall has been damaged by the infective process. Excellent results have been obtained in patients with minimal bronchiectasis secondary to aspirated foreign bodies. Following removal of the foreign body and repeated bronchoscopic aspiration of secretions, definite regression of the bronchial dilatation has been observed. Too often, however, the diagnosis is not made sufficiently early to permit such a plan of treatment. Patients commonly present themselves with well-defined bronchiectasis involving one or more pulmonary lobes or both lungs. Clerf calls attention to the fact that bronchiectasis is a common chronic pulmonary disease, being oftener observed than is pulmonary tuberculosis. Surgical extirpation of the diseased lung tissue effects a cure. All other methods of therapy are only palliative. He lays considerable stress on the importance of bronchoscopy as an aid in the prevention of bronchiectasis through the removal of bronchial obstruction. Bronchoscopic aspiration of secretions from infected areas aids patients who are too old for surgery or have bilateral lesions that render surgical treatment impractical.

In discussing the sulfonamides in relation to bronchial secretion, Norris¹⁴ states that the general effect of sulfonamide compounds is favorable, particularly when combined with bronchoscopic aspiration. He writes as follows:

We have tentatively preferred the oral method of administration because of comfort and convenience from the patient's standpoint and because its use presumably allows a much more diffuse, uniform and prolonged action than can be obtained by instilla-

The persistence of s in bronchiectasis are d It has appeared to us t attacked by combining drainage and prevents tion¹⁵ in a rather intensive course with specific antibacterial therapy. This means, in most cases, hospitalization for a period of from seven to ten days....

The concentration of sulfadiazine in bronchial secretion during oral administration is approximately 60 per cent of the blood level. This ratio is apparently not materially affected by the extent of bronchial disease or the amount of expectoration.

After intratracheal or intrabronchial instillation of 5 per cent aqueous suspension of microcrystalline sulfathiazole, cent aqueous concentrations persist in the bronchial secretion for twenty-four to forty-eight hours. The concentrations are larger, as would be expected, in cases in which there is but little expectoration.

Elimination of 2.5 per cent aqueous solution of sulfathiazole by instillation

Combined sulfonamide and bronchoscopic treatment of 10 cases of acquired bronchiectasis resulted in a con-

siderable reduction in daily sputum volume, with favorable alterations in the bacterial flora.

The plan of treatment described should prove of definite value as a preliminary to lobectomy or pneumonectomy for suppurative disease. It is probably worthy of trial in cases of well established nonsurgical bronchiectasis.

Dowling and Lepper¹⁶ have studied the toxic reactions following the use of sulfapyridine, sulfathiazole and sulfadiazine, and conclude that the optimal therapy for most infectious diseases at the present time involves the use of sulfadiazine, in low doses whenever possible but in high doses when necessary, provided there are careful regulation of fluid intake and output and frequent blood counts and urinalyses, combined with close observation of the patient.

Acute tracheobronchitis with edema. Baum¹⁷ reports that acute laryngotracheobronchitis often produces death by inflammatory edema of the subglottic tissues. Concentrated plasma is effective in reducing this edema, which it accomplishes by its high concentration and resultant osmotic action. Such action withdraws fluid from the tissues into the blood stream. It is in no way curative for the infection.

Schmidt¹⁸ calls attention to the importance of benign nontuberculous bronchial stenosis, which may develop secondary to chronic bronchial infection such as that seen in cases of chronic asthmatic bronchitis. Secondary and tertiary bronchi are principally involved, and occasionally primary bronchi. The syndrome of benign nontuberculous bronchial stenosis is a definite one. There is usually a history of antecedent pneumonia, severe tracheobronchitis or repeated seizures of asthmatic bronchitis. After variable periods, recurrent bouts of chills, fever and general malaise develop. The period of fever is usually preceded by an irritating nonproductive cough. The temperature may reach 102 to 103°F., the elevation persisting for two to seven days, at the end of which time variable amounts of purulent secretion are coughed up. This relieves the symptoms. At times the sputum is blood tinged. Bronchoscopy is the only clinical method of determining whether benign bronchial stenosis exists, and it is the only way by which such a lesion can be satisfactorily treated. In one of the cases reported, a bronchogram showed bronchiectasis of the left lower lobe in a patient forty-seven years old. Fifteen months later it had cleared up entirely so that bronchography disclosed no abnormality. In 15 of the 25 cases, bronchial stenosis was secondary to asthma or asthmatic bronchitis. In a certain number of cases the stenosis recurs and it is necessary to repeat bronchoscopic dilatation.

Asthmatoid respiration. Friedberg¹⁹ has discussed bronchoscopy with relation to asthmatoïd respiration. In 8 of his cases there was noisy breathing or wheezing, and in some of them there was a misleading familial history. A number of the cases were due to foreign bodies in the bronchus, whereas

others were due to large amounts of secretion, to bronchial stenosis or to tuberculosis. Friedberg concludes as follows:

Altered respiration of an asthmatoïd type may result from a variety of clinical conditions which produce changes in the caliber of the tracheobronchial lumen.

Pathologic narrowing of the bronchial lumen, coupled with physiologic shortening and contraction of the bronchi, probably combine to produce an abnormal vibration of the outgoing air during expiration. The resultant sound is often wheezing in character.

Illustrative cases indicate the diagnostic and therapeutic value of bronchoscopy in simulated asthmatic breathing.

Endoscopic investigation is warranted in any case of atypical bronchial asthma which does not respond readily to diagnosis and therapy.

Foreign bodies. Holinger²⁰ reports 5 cases in which confections caused severe obstruction to the airway in children. He calls particular attention to the danger of aspiration of candy or gum in children during rapid respiration. A positive history with physical findings of laryngeal, tracheal or bronchial obstruction establishes the diagnosis.

Bronchial obstruction. Having recently had 2 patients in whom aneurysm of the descending aorta was causing complete obstruction of the left main bronchus with atelectasis of the left lung, I think it is worth while to call attention to the x-ray diagnosis of such lesions by angiocardigraphy as discussed by Steinberg, Grishman and Sussman.²¹ Aortic aneurysm as a cause of bronchial obstruction is rare, but should naturally be recognized before bronchoscopy is undertaken. Bronchoscopy in aneurysm may be a harmful procedure, and biopsy of the obstructing lesion is almost certain to prove fatal.

Importance of the cough reflex. The importance of preserving the cough reflex in all diseases of the lung cannot be overemphasized. The cough is the "watchdog of the lung" and enables the patient to raise secretions that if left stagnant are definitely harmful. Many physicians, however, unnecessarily order cough medicines that seem to abolish the cough reflex. Occasionally, of course, sedation is necessary to abolish pain. In this connection Johnson²² discusses postoperative pain following total pneumonectomy. He writes as follows:

One's natural impulse is to give patients sufficient morphine to relieve the pain. However, this incurs the danger of diminishing the cough reflex to such an extent that secretions accumulate in the tracheobronchial tree. In one instance, this resulted in atelectasis of the right upper lobe after a left total pneumonectomy. Such a complication may be overcome only by the most energetic treatment.

If, on the other hand, one avoids sedation too long, the patient's life may actually be threatened as a consequence. In at least one patient, the sedation was held off too long for fear of diminishing the cough reflex. Because of pain, the patient began taking shallow rapid respirations. He allowed secretions to accumulate in his tracheobronchial tree to avoid the pain of coughing. Because of these two factors he developed an anoxia and from it went into shock. When a large dose of morphine was given, the pain was sufficiently relieved to allow the patient to cough up the secretion and take deep, even respirations. Having overcome the anoxia, the patient rapidly recovered from the shock with the aid of intravenous fluids.

It has been found therefore that one must proceed carefully alone the middle road between too much morphine and too little morphine, either extreme having potentially fatal complications. However, even with the most careful attention, it may often be impossible to reach a stage of sedation which will relieve the patient's pain adequately, and still not depress his cough reflex and respiratory rate to a dangerous degree.

Trauma. Foss and New²³ report a case of traumatic stenosis of the larynx in which the normal lumen of the larynx or upper portion of the trachea was occluded by scar tissue. This condition was treated by a new type of obturator constructed of veronite. Among the advantages of this method are that the device can be worn with comfort, that there is no formation of granulation tissue within the larynx, that there is no discharge and consequently no odor and, that the obturator may be cleaned as an office procedure.

Adenoma. Anderson²⁴ reports a case of so-called "adenoma" with metastases to the liver. The bronchial tumor alone would have been considered benign, but on the finding of metastases in the liver was diagnosed as malignant. In view of this case the author believes that the principle of treatment of bronchial adenoma should be the same as that of malignant tumor. There are undoubtedly borderline cases, but, as pointed out in last year's review¹ the term "malignant adenoma" seems to be somewhat of a contradiction in terms. Mulligan and Harper,²⁵ however, have also called attention to low-growing tumors of the bronchus originally considered to be benign adenomas but shown by later biopsies to be adenocarcinomas. Such tumors must be watched carefully. Lobectomy or pneumonectomy may be indicated in these cases, not only because of the remote possibility of histologic change to malignancy but also because of irreparable lung damage or the existence of a large extrabronchial portion of the tumor.

Carcinoma. Cohen²⁶ reports an interesting case of obstructing emphysema and atelectasis in the same lung resulting from bronchogenic carcinoma. The tumor was so situated in the main bronchus as to occlude completely the orifices of the bronchi of the upper and middle lobes; simultaneously, it caused a check-valve type of obstruction of the bronchus of the lower lobe.

Mulligan and Harper,²⁵ in a detailed study of the morphology of primary carcinoma of the human lung, have discussed the pathologic anatomy in 45 cases. In 3 cases primary carcinoma was found in both lungs, which seems quite remarkable.

Robertson²⁷ reports that carcinoma of the lung ranks in frequency second only to carcinoma of the stomach, the death rate from this condition in Scotland having increased from 437 per 100,000 in 1935 to 559 in 1940. In the 52 cases reported, 37 patients were males and 15 were females.

Further evidence of the importance of bronchogenic carcinoma is contained in an article by Overholt,²⁸ where it is stated that cancer of the lung

is one of the most serious diseases of the chest in patients within the age period from forty to sixty-five years, particularly in men; that many patients seek help at a time when the lesion is still confined to the lung; that symptoms and signs are either lacking or misleading in the early stages; that the earliest lesions in almost every case produce some telltale shadow on the x-ray film; and finally that the diagnoses may be clinched in two ways — first, the majority of lesions are visible bronchoscopically and are accessible for biopsy and, second, when the suspicion cannot be verified in this way, it is possible to explore the chest safely by surgical means, settle the diagnosis and if necessary carry out curative treatment.

Fetter²⁹ also comments on the increase in frequency of primary carcinoma of the lung as shown in recent reviews. It appears that 10 per cent of all cancers start in the lung and that it is now the second most frequent site of origin of primary malignancy, the stomach being involved more than any other organ. In the United States about 15,000 people die from bronchogenic carcinoma every year. Many factors have been considered as possible causes of the disease: the influenza epidemic of 1918 (metaplasia of the bronchial mucosa has been found in patients dying of influenza); inhalation of irritating fumes, such as the exhaust from automobiles, the fumes from tarred roads or tobacco smoke (the fact that carcinoma of the lung is at least four times as frequent in men as in women has been cited in support of the tobacco-smoke theory); silicosis; tuberculosis; and other nonspecific lung infections, such as bronchiectasis and lung abscess. The author emphasizes the importance of early bronchoscopy in suspected cases and the fact that thoracotomies should be done only by those trained in thoracic surgery.

In the early diagnosis of carcinoma of the lung, Gowar³⁰ points out the value of sputum examination by the smear method of Dudgeon. The sputum should be coughed up the first thing in the morning so that there will be no contamination with food particles. Preservatives or disinfectants must not be added, and the specimen should be examined as soon as possible after collection. Specimens collected at bronchoscopy or coughed up shortly afterward are suitable for examination. Dudgeon advised that the sputum be poured onto an unglazed porcelain tile to concentrate it, but Gowar found that by examining it in a large Petri dish on a black background it was easier to pick out portions for examination. Blood-streaked fragments or the relatively solid portions are picked out with a platinum loop or scalpel and are spread thinly on a slide. Several slides are prepared from each sputum. They are fixed by immersing at once in a bath of Schaudinn's solution, leaving them there for twenty minutes and washing them for two minutes in 70 per cent alcohol containing a trace of iodine, to

remove the excess of mercury bichloride, and then in distilled water. The slides are stained with Mayer's hemalum for one and a half to two minutes, blued in tap water, counterstained with eosin for two minutes, dehydrated and mounted in Canada balsam. They are then examined with the low power of the microscope, and any suspected group of cells is submitted to a higher magnification. When the clinical evidence is strongly in favor of carcinoma, several specimens of sputum should be examined before a negative report is made. A negative report does not exclude malignant disease. Gowar used this method in 93 cases of suspected neoplasm of the lung. In 64 per cent of the cases he succeeded in demonstrating malignant cells. The cells were found not only in advanced cases but also in a significant proportion of those in which the growth was still operable. The test is of value in establishing malignancy when other methods of investigation, including bronchoscopy, have failed, when it is desired to explore the chest, when the patient is too ill to be submitted to other methods of investigation and when the growth is masked by secondary inflammatory changes in the lung. It is urged that the test be more widely employed and that aspiration biopsy be reserved for cases giving repeatedly negative sputum tests, not being used when surgical removal of the growth is envisaged.

Field and Quilliam³¹ report the case of a four-and-a-half-year-old girl with primary bronchial carcinoma. She had always been in good health until eleven days before admission, when she developed an unproductive cough with periods of apnea. Physical examination revealed a cyanotic, dyspneic child and the presence of pleural effusion on the right, which steadily increased in spite of repeated thoracenteses. Examination of withdrawn fluid revealed many mesothelial cells suggestive of malignancy. On thoracoscopy many neoplastic nodules over the parietal pleura were seen, and histologic examination showed them to be infiltrating anaplastic carcinoma of the bronchial type. The patient expired two months after admission with evidence of metastases to the supraclavicular lymph nodes and also extension of the tumor to the chest wall. Autopsy revealed a carcinoma of the bronchus with extensive pleural involvement and metastases to the bronchial, mediastinal, right supraclavicular and axillary and celiac-plexus lymph nodes.

Metastatic pulmonary malignancy. Brezina and Lindskog³² report the case of a sixty-five-year-old woman who was submitted to right total pneumonectomy for a discrete tumor of the right upper lobe. A subtotal hysterectomy and bilateral salpingo-oophorectomy had been performed thirteen years previously for vaginal bleeding and a gross diagnosis of uterine carcinoma had been made. Recent cough and blood-tinged sputum caused the patient to seek medical help. She recovered from the operative procedure. The removed lung showed

a solitary metastasis of uterine adenocarcinoma. On examination five months later the patient was in good general condition, with no evidence of recurrence.

King and Castleman³³ made an autopsy study of bronchial involvement in metastatic pulmonary malignancy. They report as follows:

Necropsies performed at the Massachusetts General Hospital over a ten-year period on patients with metastatic pulmonary neoplasm were investigated in order to discover the incidence of those in whom actual invasion of the bronchus occurred. In 109 cases of pulmonary metastatic tumor 18.3 per cent showed bronchial invasion. In addition to these, 3 patients with malignant lymphoma showed bronchial invasion. It is believed that the incidence would have been much higher if especial attention were paid to the gross examination of the complete bronchial tree and if more sections were taken for microscopic study. Detailed analysis was made in 20 cases in which infiltration of the bronchial tree was found and the following observations were made: The neoplasm in 14 was carcinoma; in 6, sarcoma. Four patients (20 per cent) raised blood-streaked sputum. Nine patients (40 per cent) had no pulmonary symptoms.

Conclusions. Metastatic pulmonary neoplasm may simulate a primary tumor. In a patient suspected of having pulmonary neoplasm, the raising of blood-streaked sputum cannot be considered as pathognomonic of a primary tumor. But the raising of blood in a case of metastatic pulmonary neoplasm is rare. In the present study, it occurred in only 4 out of 109 cases.

Tuberculosis. After deploring the fact that many bronchoscopists are not primarily interested in bronchoscopy or diseases of the chest, Lloyd and Budetti³⁴ go on to discuss bronchoscopy in pulmonary tuberculosis. They believe that the lesion in the bronchus is the same as that in the lung, and that the healing of the intrabronchial ulcer is conditioned on the development of a negative sputum, in which event the patient shows progressive improvement in the bronchus paralleling that in the lung. In view of the underlying pathology, they say, it is difficult to see how either cauterization of ulcers or dilatation of strictures can be of much value. They are opposed to dilatation because they have never seen a permanent increase in lumen by this procedure and are afraid of possible recurrence of pain, hemoptysis and even tubercle bacilli.

Warcalde³⁵ made autopsy studies of 3 cases in which there was an association of pulmonary tuberculosis and primary cancer of the bronchus. These cases proved that tuberculosis and cancer of the lung may coexist, and the author is inclined to think that this association is more frequent than is generally believed. In 2 of his cases, cancer had developed in a bronchus that had been chronically damaged by material eliminated from an old tuberculous cavity. In the third case, there was malignant degeneration of an old tuberculous cavity that had been partially epithelialized. These cases, as well as others cited from the literature, prove that chronic tuberculosis may bring about changes in the tissues from which cancer may develop. Nevertheless, tuberculosis cannot be considered a precancerous disease, nor is it true, as Ewing claimed,

that chronic tuberculosis is the chief cause of cancer of the lung. Warcalde goes on to say that there is no doubt that cancer may bring about exacerbation of old tuberculous lesions of the lung. This, too, was seen in these cases. Paradoxically, tuberculous lesions may disappear in the course of cancer. In one of these cases tuberculous tissue had been destroyed by the advancing cancer, and he cites a case described by Frommel in which no tuberculous tissue was found in the lungs of a patient dead of bronchial cancer who during life had repeatedly shown tubercle bacilli in the sputum. The cancer had destroyed both normal and tuberculous tissue after having caused exacerbation of the tuberculosis.

Tuttle, O'Brien, Day and Phillips,³⁶ in a study of 92 patients with ulcerobronchial or healed bronchial stenosis, made the following observations:

Thirty-two per cent of this group are dead. Thirty-three per cent are still classified as unstable. Sixty-nine patients had ulcerostenosis when first seen. The ulcerative lesion was treated with 30 per cent silver nitrate. Seventy per cent of the group healed while 30 per cent did not change or become worse. Pneumothorax as a method of controlling the parenchymal processes has been compared with thoracoplasty. Pneumothorax was adequate in only 12 of the 47 instances in which it was used. The incidence of empyema and unexpanded lungs is high (31.9 per cent and 46.7 per cent, respectively). Thoracoplasty has yielded results superior to pneumothorax.

During the past year several articles have appeared on lobectomy and pneumonectomy for tuberculosis. Churchill and Klopstock³⁷ report 6 cases of pulmonary tuberculosis, 3 of which provided orthodox indications for resection of the lesion by lobectomy. Three others presented the usual indications for thoracoplasty but lobectomy was performed by election. Healing per primam resulted in all cases. Lobectomy provides a more selective and immediate method of eradicating certain lesions of tuberculosis than does collapse therapy. It may be used subsequent to artificial pneumothorax, thereby restoring to that procedure the reputation of finesse that it should enjoy. A method of treatment that combines conservation of lung function with immediate conversion of the sputum and a shortening of the span of cancer cannot be dismissed until its scope has been more fully explored. All patients were subjected to bronchoscopy preoperatively to rule out

ulceration in the trachea and sometimes in the bronchus

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 30211

PRESENTATION OF CASE

A fifty-one-year-old machinist entered the hospital because of shortness of breath and productive cough.

The patient was in excellent health until one month before admission, when he developed a heavy cold characterized by malaise and cough, the latter usually occurring after returning from work in the evening and being relieved by the raising of a plug of greenish sputum. He felt so poorly that he stayed out of work for three or four days, during which time there was no change in his symptoms. He then returned to work but was weak and short of breath. He collapsed and was taken home, where he rested for ten days. He was then admitted to a community hospital, where x-ray studies were done and about 1500 cc. of fluid was removed from his chest, with considerable relief. He was discharged at the end of eight days under the care of a roentgenologist, who gave him "high-frequency" x-ray treatment every other day for a few days, without relief. The treatment was stopped and he became progressively more dyspneic. There was no chest pain, hemoptysis or known weight loss. For two months before the onset of his illness he had been constipated and had noted a decrease in the caliber of his stools. The abdomen became more protuberant and he experienced occasional transient crampy pain in the abdomen. He had no nausea, vomiting, loss of appetite or clay-colored or tarry stools.

Physical examination showed a well-developed, well-nourished, dyspneic man. The neck was "swollen" on both sides. The heart was not remarkable. There was dullness over the entire left chest, with decreased breath sounds, bronchial breathing and absent tactile fremitus. The abdomen was distended, with a fluid wave and shifting dullness.

The blood pressure was 130 systolic, 80 diastolic. The temperature was 99°F., the pulse 100, and the respirations 25.

Examination of the blood showed a red-cell count of 3,200,000, with 90 per cent hemoglobin. The white-cell count was 11,500, with 92 per cent neutrophils, 6 per cent lymphocytes and 2 per cent mono-

cytes. The urine was normal. A blood Hinton test was negative.

X-ray examination revealed a large amount of fluid in the left pleural cavity, which compressed the left lung and displaced the heart and mediastinum to the right (Fig. 1). There appeared to be widening of the superior portion of the mediastinum on the right. The right lung field was fairly clear, with some increase in the markings. A small amount of fluid was seen in the right costophrenic angle. A barium enema was unsatisfactory because of inadequate preparation, but no abnormality of the colon could be demonstrated. The liver was somewhat enlarged. Thoracentesis in the left seventh interspace yielded 2400 cc. of watery, red fluid with a specific gravity of 1.011. A culture was negative, and no tumor cells were seen in the sediment. Following this procedure the patient improved considerably but temporarily. A second thoracentesis two days later yielded 750 cc. of similar fluid, but the dyspnea increased and he died on the fourth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. REED HARWOOD: I take it that this patient did not have a cold. There is no mention of sore throat or coryza. I also presume that the radiologist in the outside hospital was able to see something after the chest tap that gave him an idea concerning the diagnosis. Our x-ray films are not definite enough to justify a diagnosis.

It is not clear from the history when the swelling of the abdomen took place.

The description of the cervical swelling could mean anything, or nothing. Did it mean masses, was this actual edema of the neck or was it simply due to distended jugular veins?

DR. FRANK WHELOCK: The swelling was at the base of the neck in the midline, extending down to the shoulder. It was fairly firm, but not a mass; just a swollen neck.

DR. HARWOOD: Was the bronchial breathing heard throughout the whole chest or simply near the upper level of the fluid?

DR. WHELOCK: It was above the level of the fluid.

DR. HARWOOD: There must have been absent breath sounds low on the left side.

This man died soon after admission and presumably never had a bowel movement after entrance to the hospital, but with a story of crampy abdominal pain and decrease in the caliber of the stools, a test for occult blood in the stool would have been important.

DR. BENJAMIN CASTLEMAN: Blood examination at the outside hospital showed a red-cell count of 4,100,000, with 80 per cent hemoglobin.

DR. HARWOOD: We might see the x-ray films at this point.

*On leave of absence

DR. LAURENCE L. ROBBINS: As is fairly evident, there is a large amount of fluid in the left pleural cavity displacing the heart and mediastinum to the right. There is a small amount of fluid in the right pleural cavity. I cannot tell much about the left lung. These films are suspicious of some disease within the lung, but it is indefinite on account of the fluid. A fairly important observation is the appearance of the right side of the superior mediastinum, which is large and somewhat lobulated in out-

the lung was pushed anteriorly. There is no evidence of the mass extending up into the neck. Everything has been pushed over to the right.

DR. HARWOOD: Do you think the tumor alone has produced this angulation?

DR. ROBBINS: I think that that is sufficient reason to explain it.

DR. HARWOOD: The outstanding feature of this case is the rapidity with which the patient died. There is little in the way of symptoms on which



FIGURE 1. Roentgenogram of Chest.

line. The right lung is probably clear. It has a peculiar appearance, which is probably due to compression from the displaced mediastinum.

On taking a quick look at the films of the barium enema, I do not believe there is much information to be obtained from them. The patient was not particularly well prepared.

DR. HARWOOD: This shadow here is perhaps the mediastinal tumor.

DR. ROBBINS: I do not believe that we have any way of knowing. Perhaps the patient was in a horizontal position for some time, and as the fluid accumulated in the posterior portion of the chest,

to make a diagnosis until just a month before his death. I believe that he died of a malignant neoplastic disease, but I admit that I have little idea of what form of malignant disease it was.

It seems highly unlikely that this could have been an infection. With bloody pleural fluid and ascites, one might consider a generalized tuberculous infection. The patient, however, had no fever, and the disease was much too rapid in its downhill course.

The malignant diseases that we should consider are carcinoma, fibrosarcoma and some type of lymphoma. Before seeing the x-ray films, I did

not realize that the mediastinal lymph nodes were as enlarged as they seem to be on this x-ray film, and I considered carcinoma as the likeliest diagnosis. The question is, Where did it arise? We have one hint in the abdominal symptoms that he had. Did he have carcinoma of the colon? I am inclined to think not. I may be reasoning erroneously when I say that carcinoma of the colon is usually slowly growing, with metastases manifesting themselves late. I am going to rule it out.

Did he have carcinoma of the liver? The liver was enlarged, and that is the only single finding we have to implicate the liver. There were no abdominal masses and no jaundice. I am going to exclude the liver as the possible site of the tumor.

Did he have carcinoma of the stomach? The outstanding complaint might have been due to carcinoma high in the fundus. Carcinoma of the fundus occasionally goes unsuspected until metastases occur. He could easily have had metastases both to the peritoneum and to the lung and pleura.

Carcinoma of the lung must be considered, of course. He could have had a small carcinoma in a silent area of the lung, arising from a small bronchus so that, while the tumor grew, it did not invade a large bronchus to produce cough, hemoptysis and wheezing; then, as it approached the pleura, it might have produced pleural effusion and also metastases, both to the mediastinal lymph nodes and to the peritoneum. That is unusual, but I have an idea that this case is unusual, which is why it was presented.

Another possibility is that he had lymphoma—a generalized lymphomatous disease—with the most obvious manifestations in the mediastinal lymph nodes. The first real symptom might have been the cough, which suggests that the mediastinal tumor was pressing on the left main bronchus and that the mediastinal tumor grew to considerable size before producing definite symptoms.

I am at a loss to decide which of these attractive possibilities to choose, but I am going to place as my first bet lymphosarcoma of the mediastinal lymph nodes, pleura and peritoneum, and as the second bet, carcinoma of the lung, with metastases to the pleura and peritoneum. There is one possibility that I might mention, although I have no great confidence in it. With the mediastinum so involved, the inferior as well as the superior vena cava might have been pressed on by the tumor, producing, as it could easily, enlargement of the liver and ascites. Against that possibility is the fact that he had no peripheral edema.

DR. JOSEPH C. AUB: Could the patient have died from replacement of the mediastinum to the left following the removal of the fluid? What does the mediastinal syndrome come from?

DR. ROBBINS: I think that it is due to pressure of the tumor rather than to that of the fluid itself. I do not recall having seen an upper mediastinal syndrome produced by fluid.

DR. AUB: I mean that death occurred because of replacement of the mediastinum to normal after the removal of the fluid. Why does it happen? It does.

DR. JACOB LERMAN: Death under those circumstances would be extremely rapid. This man lived for practically two days.

DR. CASTLEMAN: One interesting point is that, while the patient was in the hospital, the left arm became swollen quite suddenly and markedly. Dr. Harwood, have you any further impression?

DR. HARWOOD: The fact does not seem to have any diagnostic importance. We know that he had enlarged mediastinal lymph nodes. Swelling of either arm, the face or the neck can occur at any time with an expanding mediastinal lesion.

CLINICAL DIAGNOSIS

Mediastinal tumor, with extension to lung.

DR. HARWOOD'S DIAGNOSIS

Lymphosarcoma of mediastinal lymph nodes, pleura and peritoneum, with metastases?

Bronchiogenic carcinoma, with metastases to mediastinal lymph nodes, pleura and peritoneum?

ANATOMICAL DIAGNOSES

Oat-cell carcinoma of left lung, with extension to trachea, pleura and pericardium, with compression and thrombosis of left subclavian vein and with metastases to the vertebrae.

Hemothorax, bilateral.

Pulmonary atelectasis, left.

Bronchopneumonia, right lower lobe.

Peripheral edema of arms.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy on this man showed a large nodular mediastinal mass, which was believed to be involved lymph nodes. The mass extended upward about 3 cm. into the suprasternal notch, inferiorly to cover the upper third of the external surface of the pericardium and then to the left to involve the pleura of the left lung all along the hilus. When we cut across the mass we could see that it surrounded the aorta, the left subclavian vein and the right side of the superior vena cava. All the structures in that region were compressed but apparently not infiltrated by the tumor. The left subclavian vein was thrombosed. Because the superior vena cava was merely compressed rather than infiltrated, we thought that the best diagnosis was some form of malignant lymphoma, since carcinoma is usually infiltrative.

On opening the trachea and bronchi we found that there was extensive involvement of the left main bronchus with tumor, but the lumen was still patent. The mediastinal nodes surrounding the trachea

had penetrated the trachea in one place to form an intrinsic mucosal plaque of tumor 1 cm. long and 3 mm. wide. It is interesting that in so doing the tumor, as is usual, surrounded the cartilaginous plates but had not destroyed them. The tumor had extended into the lung parenchyma.

On microscopic examination the tumor proved to be an oat-cell carcinoma of the lung. The only other metastases found, in addition to the mediastinal lymph nodes, were in the vertebrae, which were almost completely replaced by tumor, and one certainly should have expected severe myelophthisic anemia.

DR. HELEN PITTMAN: Did he have ascites?

DR. CASTLEMAN: No.

CASE 30212

PRESENTATION OF CASE

A sixty-six-year-old housewife entered the hospital because of severe pain in the right leg.

The patient was known to have been hypertensive for many years. For several months before entry she had "palpitation" and had been given 3 gr. of quinidine four times daily. She had been in fairly good health for the preceding two or three weeks and was able to carry on with the usual housework. Early one evening, about twenty-two hours before admission, she was suddenly seized with an intense, substernal pain in the chest, which radiated to the right midback and was aggravated by inspiration. She felt that she could not breathe. The pain was followed almost immediately by intense pain in the right leg, extending from the hip to the foot. The leg felt completely numb and she could not move it. She was seen by her physician who found her in shock — cold and clammy. The pulse was 120 and regular. The blood pressure, which had been around 250 systolic, 190 diastolic, was 200 systolic, 110 diastolic. There was no fever. After the onset of pain in the leg, the pain in the chest practically disappeared and she was able to breathe without difficulty. This, however, may have been due to the fact that the former was so severe that the latter was ignored. She was given $\frac{1}{2}$ gr. of morphine through the night and the next morning, without relief. She perspired considerably, but voided little urine. She had had "virus pneumonia" three or four months prior to admission, followed by a chronic productive cough and by general sinus infection.

Physical examination showed a well-developed, well-nourished, sallow patient who appeared to be critically ill and complained bitterly of pain in the right leg. The leg was swollen, cold, "anesthetic and paretic," with mild grayish cyanosis involving the entire extremity; no arterial pulsation could be felt. She could not wiggle her toes. The heart was enlarged, the left border of cardiac dullness being 10 cm. to the left of the midline in the fifth space.

The sounds were regular. A rough, distant, systolic murmur, loudest at the apex, was heard by one observer. Examination of the lungs was unsatisfactory. The abdomen was negative.

The blood pressure was 110 systolic, 60 diastolic, in the right arm, and 115 systolic, 60 diastolic, in the left. The pulse was 92. The temperature and respirations were normal.

The patient was given $\frac{1}{4}$ gr. of morphine every three hours and $\frac{1}{2}$ gr. of papaverine every four hours. A lumbar paravertebral novocain injection was performed in the right first, second and third lumbar regions without any objective or subjective change in the leg. About ten hours after admission rectal bleeding was noted. The pulse rose to 110, the respirations were 30, and the blood pressure fell rapidly. There was some bloody sputum, and the patient died a few minutes later.

DIFFERENTIAL DIAGNOSIS

DR. WYMAN RICHARDSON: The story as we are given it here seems to me definite and quite pathognomonic. I know of no condition that produces intense chest pain followed shortly by terrific pain in the leg other than a dissecting aortic aneurysm, and that seems to me the only possible diagnosis in this case.

The heart examination is not particularly specific although there may have been varying murmurs; at least the suggestion here is that the murmur was heard by only one observer and was loud. Physical examination corroborates the diagnosis of dissecting aortic aneurysm.

In regard to other possible diagnoses, I am so sure about this that it looks as if I might be riding to a fall; although I do not see how the diagnosis can be anything else. If one has to make another diagnosis, one must contemplate something that will produce intense chest pain and obstruction to the right iliac artery or some large artery of the leg. If one is considering the possibility of a venous embolus, there might be intense chest pain with a pulmonary embolus. I suppose it is conceivable that one could have a paradoxical embolus to the right iliac artery, but it would have to be a big patent foramen ovale to allow the embolus to get through; and that seems hardly worth considering. The only other thing I can think of is a silent coronary occlusion with a myocardial infarct, followed by a mural thrombus; then a second myocardial infarct, this one not silent, producing severe pain in the chest and at the same time dislodging the previous thrombus and sending it to the iliac artery. This also seems to be an almost impossible coincidence. Otherwise I cannot think of any condition that would produce intense pain in the chest and would occlude the right iliac artery.

Regarding the laboratory findings, I am interested for my own benefit to know — possibly Dr. Castleman does not have this knowledge — whether there

was increased leukocytosis. One would expect that with a dissecting aneurysm, where blood is being disseminated through tissues not used to having a lot of free blood in them, there would be considerable leukocytosis.

DR. BENJAMIN CASTLEMAN: No blood count is recorded.

DR. RICHARDSON: I thought that might be the case.

The other thing I want to speak of is the matter of therapy. Evidently the hope was that a good deal of the difficulty with circulation in the leg was due to secondary spasm; hence, efforts were made to relieve the secondary spasm of the artery. I do not believe that the method employed would have been particularly successful. There is one procedure I can think of — and it has been attempted¹ — that might relieve the whole situation, namely, to open the iliac artery and also to make an opening in the dissecting aneurysm, so that the pressure from the arterial system is relieved, as sometimes happens spontaneously. This may produce a remission, often of considerable duration. We had a case on the ward some years ago in which I took great pride in making a diagnosis of dissecting aneurysm. The patient got well, and subsequently this diagnosis was discarded. I am taking this opportunity to brag about the fact that this patient, who died several years later, did have a dissecting aneurysm that had evidently dissected some years before. In the present case, as I said before, I cannot see how the diagnosis can be anything other than dissecting aortic aneurysm.

There remains one thing to discuss — the manner of the patient's death. As you probably all know, these patients often die of cardiac tamponade, owing to the leakage of blood into the pericardial sac or around the coronary arteries, with pressure on the coronary arteries and a final rupture into the pericardial sac with cardiac tamponade. That seems the likely reason for this patient's death. It ought to be mentioned that such patients sometimes develop anuria due to pressure around the renal arteries, with renal ischemia. Hematuria is not an uncommon finding in these cases.

The pathological findings also might be discussed. There is usually a cystic necrosis of the aorta. I believe that this condition may arise from a purely atheromatous lesion, and there may be reason to doubt whether this patient actually did have cystic disease of the aorta. If, however, one is to bet on chance it is much better to say that there was cystic degeneration of the aorta. I cannot think of any incidental findings that may be found. One might say that in patients of this age it probably is a better procedure to try to think of all the various pathologic lesions that there might have been, because one often finds a great many different lesions occurring in such patients, and I am rather inclined to disagree with Dr. Cabot's dictum, namely, that

one should make one diagnosis fit all the symptoms. In this case, with the symptoms given, I can think of but one diagnosis that fits all the symptoms and that is dissecting aortic aneurysm.

DR. CASTLEMAN: Does anyone want to quiz Dr. Richardson?

A PHYSICIAN: How does he explain the bloody stools?

DR. RICHARDSON: I meant to mention the bloody stools. I do not explain them on the basis of aortic aneurysm. It seems conceivable that there might have been sufficient interference with the arterial supply to the lower rectum, in the same manner that there was interference to the supply of the blood to the leg, so that there was an ischemia or infarct involving the lower bowel.

DR. CHESTER M. JONES: Could you not have interference with the inferior mesenteric vessels, with probably an infarct in the region that they supply?

DR. RICHARDSON: Yes; I thought that might explain it. I do not know why, but I have a hunch that the pathologist will not be able to explain the bloody stools.

CLINICAL DIAGNOSIS

Dissecting aneurysm?

DR. RICHARDSON'S DIAGNOSIS

Dissecting aortic aneurysm.

ANATOMICAL DIAGNOSES

Dissecting aneurysm of aorta, with involvement of the major branches and occlusion of the right common iliac artery.

Pulmonary hemorrhage, bilateral.

Hemothorax, bilateral.

Hemopericardium.

Hemoperitoneum, slight.

Cardiac hypertrophy, hypertensive type.

Early infarction of intestine?

Arteriosclerosis, generalized.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy on this patient showed what Dr. Richardson predicted. This patient did have an aortic dissection. The physician in charge of this case reasoned the same way, but he was not so sure of his diagnosis. In the first place the hypertension did not remain up, as it does in the majority of cases. In this case the blood pressure had fallen.

DR. RICHARDSON: The blood pressure does not fall in the majority of cases?

DR. CASTLEMAN: In most of the cases that we have had here, the blood pressure has remained elevated.

DR. C. SIDNEY BURWELL: That is true. It is one of the differential points between coronary thrombosis and aortic dissection.

DR. CASTLEMAN: In about 80 per cent of our cases the pressure remained elevated,² and the man in charge of this patient thought that that was one point against dissecting aortic aneurysm. He also thought that the patient should have continued to have at least some pain in the chest, which apparently she did not have after the initial attack.

At autopsy the heart was slightly enlarged and of the hypertensive type. In the arch was the intimal tear, a horizontal one that involved one third of the circumference of the aorta. There was only a slight to moderate amount of arteriosclerosis, but the intimal tear did not arise on an atheromatous plaque—in fact it very rarely, if ever, does. The tear went through the intima and two thirds of the way through the media, dissecting proximally to the annulus of the aortic valve and distally down the whole length of the abdominal aorta, first into the carotid and innominate arteries and then into both renal arteries (Fig. 1). The dissection around the mouths of both renal arteries accounted for the anuria. It extended into the right iliac artery, elevating the intima and producing a complete occlusion. It also dissected into the openings of the celiac axis and the inferior and superior mesenteric vessels. The small bowel was completely filled with blood and showed early gangrene.

The external perforation of the aneurysm was not too clear. We found only 250 cc. of blood in the pericardial cavity, much less than one sees with rupture of the adventitia that produces cardiac tamponade, which was not present. There was also about 200 cc. of blood in each pleural cavity, but here again there was no definite external rupture of the adventitia. Blood was present in the adventitia of the main pulmonary arteries and extended into the lungs so that we found hemorrhage into both lungs, a condition that we have seen twice before. I suppose the patient really died because of the slow oozing of blood throughout all parts of the aorta.

Microscopic examination of the aorta showed medial degeneration.

DR. RICHARDSON: Were the coronary arteries dissected?

DR. CASTLEMAN: No.

DR. RICHARDSON: Do you suppose that the extensive involvement of the leg could have accounted for the drop in blood pressure?

DR. BURWELL: The amount of blood that the patient had lost might have accounted for it.

DR. CASTLEMAN: This case would probably have not been a good one on which to try the iliac-artery

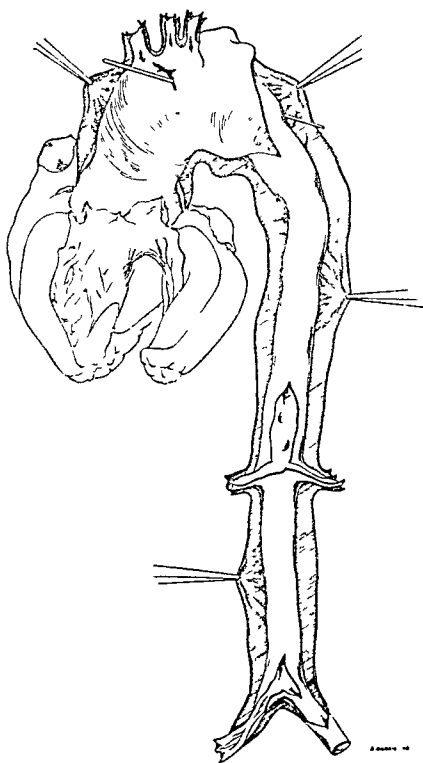


FIGURE 1. Drawing Showing the Extent of the Dissecting Aneurysm.

operation that Dr. Richardson mentioned. The patient was much too sick.

DR. BURWELL: Has that really been done?

DR. CASTLEMAN: Not here, but it has been tried in New York City, as I have already mentioned. The patient died six days after operation.

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PENICILLIN

THANKS to the initiative and enterprise of certain pharmaceutical houses and other industrial plants, supplies of penicillin have increased to such a point that the drug is about to be released for more extensive civilian use than has been possible during the past year. Up to this time only a limited quantity has been available for emergency civilian use in connection with the War Production Board through the committee of the National Research Council. Greater amounts are now on hand, allocation may be continued by the War Production Board by an advisory panel representing the National Research Council, the United States Army, Navy, Service and the American Medical Association.

To aid in the proper storage and distribution of penicillin, a list of "depot hospitals" has been prepared by the Office of Civilian Penicillin Distribution of the War Production Board, those selected for New England being designated elsewhere in this issue of the *Journal*. Each hospital will be permitted to purchase a monthly quota, and other hospitals in its vicinity will be allowed to obtain their supplies through this depot.

The responsibility for the intelligent civilian use of this new drug now rests in the hands of practitioners, and they should not fail to realize that the supply is still limited. Penicillin has been proved capable of remarkable therapeutic results; on the other hand, its indiscriminate use in all types of infection will result in a shortage for the treatment of the very type of case in which a cure may be expected.

PHYSICAL MEDICINE

THE gift of \$1,100,000 by Bernard M. Baruch to sponsor the development of teaching and research in physical medicine comes at a particularly opportune time. In the physical rehabilitation of wounded and ill soldiers and sailors and victims of industrial accidents, as well as of the young and old suffering from disabilities of locomotion, physical and occupational therapy is destined to play an important role. Mr. Baruch's interest in physical therapy arose because of his father Dr. Simon Baruch, a prominent hydrologist and a pioneer in this field, and was further stimulated by a desire to aid disabled war veterans. His decision to benefit physical medicine, however, was dependent on the results of a thorough scientific exploration of the subject. To accomplish this a committee under the chairmanship of Dr. Ray Lyman Wilbur and directed by Dr. Frank H. Krusen was formed. Nine subcommittees were also appointed, including those dealing with the subjects of poliomyelitis, occupational therapy, prevention and body mechanics, hydrology and health resorts, clinical and basic research, rehabilitation and teaching. Over four hundred scientists were consulted in the course of a comprehensive three-month survey. The final report, seeking to emulate those famous reports of Mr. Baruch for which he

became known as "Mr. Facts," is a valuable source of information on the multiple aspects of physical medicine

This report emphasizes the wide scope of physical medicine and its possible application in nearly all fields of medical practice. Physical agents produce striking biologic responses and psychic reactions, which in potency compare favorably with those of drugs and other established therapeutic procedures. In order that these agents may be widely recognized and used the primary step in development is considered the education of teachers and specialists in physical medicine. This is to be accomplished by establishing key centers in selected medical schools where, through basic and clinical research, a background of scientific knowledge will be accumulated. Teachers will be trained in these centers who, in turn, will go to the medical schools of the country to educate future physicians in what are considered to be the important essentials of physical therapy. A supply of specialists will also become available to aid in postwar physical rehabilitation. The center at the College of Physicians and Surgeons, Columbia University, will serve as the chief training center where all phases of physical medicine will be developed and co-ordinated, including electronics, hydrology, climatology, manipulative procedures and occupational therapy. Hydrology and spa therapy will be the major concern of another center, and at the third, the structural mechanics of the body will be studied. An important aspect of this will be a careful scientific analysis of nonmedical, therapeutic procedures and claims by practitioners of osteopathy, chiropractic and naturopathy.

Extensive fundamental studies must be made, and results cannot be expected at once. Scientific data are accumulated only slowly and painstakingly. The wisdom of setting up these centers on a ten-year basis is thus apparent. It is reasonable to expect, however, that proper recognition and an increased use of physical medicine will be achieved in a fairly short time. The full benefits of this million-dollar gift will not be apparent until physical medicine is firmly established on a scientific basis by this preliminary period of research. The future practice of medicine will then be influenced by the widespread instruction of medical students in the procedures of

physical therapy that have proved to be worth while. Provided that the work at the key centers is successfully carried out with the active co-operation of the medical faculties and that the anticipated results are obtained still greater projects, already outlined in the original report of the committee, have been promised similar financial aid. One envisions an important step in the progress of medicine accelerated by Mr. Baruch's perceptive philanthropy.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

WENTWORTH — Mark H. Wentworth, M.D., of Concord died May 15. He was in his sixty-sixth year.

Dr. Wentworth received his degree from Harvard Medical School in 1905. He was a member of the Massachusetts Medical Society, the American Medical Association, the Boston Surgical Society and the New England Pediatric Society.

His widow, two daughters and two grandchildren survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MARCH, 1944

RESUME

DISEASES	MARCH 1944	MARCH 1943	SEVEN YEAR MEDIAN
Anterior poliomyelitis	0	2	0
Chancroid	2	2	**
Chicken pox	3364	1604	1471
Diphtheria	25	7	12
Dog bite	739	706	754
Dysentery bacillary	19	4	3
German measles	313	8210	103
Gonorrhea	509	327	327
Lymphogranuloma venereum	5	**	**
Measles	3546	6416	3245
"	68	118	103
"	4	2	2
"	7	2	*
"	0	0	*
"	2	2	*
"	1	4	*
"	17	12	*
"	1576	1077	1077
Pneumonia, lobar	423	372	609
Salmonella infections	13	2	2
Scarlet fever	1915	2494	1184
Syphilis	674	479	479
Tuberculosis pulmonary	267	283	286
Tuberculosis other forms	22	18	27
Typhoid fever	3	0	3
Undulant fever	3	1	3
Whooping cough	378	874	969

*Pfeiffer bacillus meningitis only other form reportable previous to 1941
**Made reportable December, 1943

COMMENT

Diphtheria remained relatively high — twice the seven-year median, — although the disease was below the level of the last two months of 1943.

Meningococcal meningitis was at a point almost seven times the seven year median but was much below the level of March of last year. Nevertheless, the total number of cases for the first three months of this year exceeded that for the corresponding period of last year.

The thirteen cases of salmonella infections represent a new high for March. They were not widely distributed, however, seven of them occurring in one city.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Actinomycosis was reported from Palmer, 1, total 1.
Diphtheria was reported from Boston 5, Cambridge, 1, Lawrence, 15, Lowell, 1, Mattapoisett, 1, Methuen, 1, Salem, 1, total, 25.

Dysentery, amebic, was reported from: Fort Devens, 1; total, 1.

Dysentery, bacillary, was reported from: Boston, 2; Worcester (State Hospital), 17; total, 19.

Encephalitis, infectious, was reported from: Braintree, 1; total, 1.

Lymphocytic choriomeningitis was reported from: Springfield, 1; total, 1.

Malaria was reported from: Boston, 1; Camp Edwards, 14; Cushing General Hospital, 7; Fall River, 1; Fort Banks, 11; Fort Devens, 20; Haverhill, 4; Millbury, 1; Milton, 1; Newburyport, 1; Plymouth, 1; U. S. Marine Hospital (Boston), 1; total, 63.

Meningitis, meningococcal, was reported from: Agawam, 1; Arlington, 2; Ashland, 1; Attleboro, 1; Ayer, 1; Boston, 19; Braintree, 2; Brockton, 2; Camp Edwards, 2; Cambridge, 2; Chelsea, 1; Chicopee, 1; Everett, 1; Fall River, 3; Fort Devens, 2; Franklin, 1; Lexington, 1; Lowell, 2; Malden, 1; Marblehead, 1; Middleboro, 1; Milford, 1; Milton, 3; Newton, 2; Norton, 1; Pittsfield, 1; Quincy, 1; Saugus, 1; Shrewsbury, 1; Somerville, 1; Sturbridge, 1; Waltham, 1; Watertown, 2; Westfield, 2; West Springfield, 1; Worcester, 1; total, 68.

Meningitis, Pfeiffer-bacillus, was reported from: Brockton, 1; New Bedford, 1; Weymouth, 2; total, 4.

Meningitis, pneumococcal, was reported from: Boston, 2; Cambridge, 1; Cohasset, 1; Norwood, 1; Salem, 1; Worcester, 1; total, 7.

Meningitis, streptococcal, was reported from: Lawrence, 1; New Bedford, 1; total, 2.

Meningitis, other forms, was reported from: Boston, 1; total, 1.

Meningitis, undetermined, was reported from: Boston, 3; Cambridge, 2; Chelsea, 1; Holyoke, 1; Quincy, 5; Westfield, 2; Worcester, 3; total, 17.

Salmonella infections were reported from: Attleboro, 1; Bedford, 1; Dartmouth, 1; Lynn, 1; Manchester, 1; Medford, 1; Newton, 7; total, 13.

Septic sore throat was reported from: Amesbury, 1; Bedford, 1; Boston, 9; Bourne, 1; Cambridge, 1; Camp Edwards, 4; Haverhill, 2; Lawrence, 3; Merrimac, 8; Newbury, 1; Newton, 2; Scituate, 1; Winchester, 1; Worcester, 2; total, 37.

Tetanus was reported from: New Bedford, 1; Quincy, 1; total, 2.

Trichinosis was reported from: Boston, 3; Chelsea, 3; total, 6.

Typhoid fever was reported from: Fall River, 1; New Bedford, 1; North Attleboro, 1; total, 3.

Undulant fever was reported from: Boston, 1; Cambridge, 1; Winchester, 1; total, 3.

MISCELLANY

DEPOT HOSPITALS FOR PENICILLIN

The following New England institutions have been selected to serve as "depot hospitals" by the Office of Civilian Penicillin Distribution, War Production Board, for the proper storage and distribution of penicillin for civilian medical use. These hospitals will be the local depots for further distribution of the drug, as well as a source of supply for their own requirements. They will recognize the request of other hospitals and, if the need is established, will, to the best of their ability in consideration of their supply on hand, furnish penicillin for purchase by such other hospitals. This list is subject to revision by action of the Advisory Panel.

CONNECTICUT

<i>Bridgeport.</i> Bridgeport Hospital St. Vincent's Hospital	<i>New Haven.</i> Grace Hospital Hospital of St. Raphael New Haven Hospital
<i>Bristol.</i> Bristol Hospital	<i>New London.</i> Lawrence and Memorial Associated Hospital
<i>Danbury.</i> Danbury Hospital	<i>Norwalk.</i> Norwalk General Hospital
<i>Hartford.</i> Hartford Hospital Municipal Hospitals St. Francis Hospital	<i>Norwich.</i> William W. Backus Hospital
<i>Meriden.</i> Meriden Hospital	<i>Torrington.</i> Charlotte Hungerford Hospital
<i>Middletown.</i> Middlesex Hospital	<i>Waterbury.</i> St. Mary's Hospital Waterbury Hospital
<i>New Britain.</i> New Britain General Hospital	

MAINE

<i>Augusta.</i> Augusta General Hospital	<i>Portland.</i> Maine General Hospital Mercy Hospital
<i>Bangor.</i> Eastern Maine General Hospital	<i>Presque Isle.</i> Presque Isle General Hospital
<i>Dover-Foxcroft.</i> Mayo Memorial Hospital	<i>Rockland.</i> Knox County General Hospital
<i>Lewiston.</i> Central Maine General Hospital St. Mary's General Hospital	<i>Rumford.</i> Rumford Community Hospital

MASSACHUSETTS

<i>Beverly.</i> Beverly Hospital	<i>Greenfield.</i> Franklin County Public Hospital
<i>Boston.</i> Beth Israel Hospital Boston City Hospital Carney Hospital Children's Hospital Faulkner Hospital Massachusetts General Hospital Massachusetts Memorial Hospitals New England Deaconess Hospital New England Hospital for Women and Children Peter Bent Brigham Hospital St. Elizabeth's Hospital	<i>Lawrence.</i> Lawrence General Hospital
<i>Brockton.</i> Brockton Hospital	<i>Lowell.</i> Lowell General Hospital St. John's Hospital St. Joseph's Hospital
<i>Cambridge.</i> Cambridge City Hospital Cambridge Hospital	<i>Lynn.</i> Lynn Hospital
<i>Chelsea.</i> Chelsea Memorial Hospital	<i>New Bedford.</i> St. Luke's Hospital
<i>Fall River.</i> Truesdale Hospital Union Hospital	<i>Northampton.</i> Cooley Dickinson Hospital
<i>Fitchburg.</i> Burbank Hospital	<i>Pittsfield.</i> House of Mercy Hospital St. Luke's Hospital
<i>Framingham.</i> Framingham Union Hospital	<i>Quincy.</i> Quincy City Hospital
	<i>Salem.</i> Salem Hospital
	<i>Springfield.</i> Mercy Hospital Springfield Hospital Wesson Memorial Hospital
	<i>Worcester.</i> Memorial Hospital St. Vincent Hospital Worcester City Hospital Worcester Hahnemann Hospital

NEW HAMPSHIRE

<i>Berlin.</i> St. Louis Hospital	<i>Keene.</i> Elliot Community Hospital
<i>Concord.</i> Margaret Pillsbury General Hospital	<i>Manchester.</i> Elliot Hospital Sacred Heart Hospital
<i>Hanover.</i> Mary Hitchcock Memorial Hospital	<i>Nashua.</i> Nashua Memorial Hospital
	<i>Portsmouth.</i> Portsmouth Hospital

RHODE ISLAND

<i>Newport.</i> Newport Hospital	<i>Providence.</i> Homeopathic Hospital Rhode Island Hospital St. Joseph's Hospital
<i>Pawtucket.</i> Memorial Hospital	<i>Westerly.</i> Westerly Hospital

VERMONT

<i>Bennington.</i> Henry W. Putnam Memorial Hospital	<i>Newport.</i> Orleans County Memorial Hospital
<i>Burlington.</i> Bishop De Goesbriand Hospital Mary Fletcher Hospital	<i>Rutland.</i> Rutland Hospital
<i>Montpelier.</i> Heaton Hospital	<i>St. Albans.</i> St. Albans Hospital
	<i>St. Johnsbury.</i> Brightlook Hospital

NOTICES

PHI DELTA EPSILON LECTURE

Dr. Edward Weiss, professor of medicine at Temple University School of Medicine, will deliver the first annual Phi Delta Epsilon lecture at Boston University School of Medicine auditorium, on Wednesday, May 31, at 8:15 p.m. His topic will be "Psychosomatic Aspects of Cardiovascular Diseases." He will be introduced by Dr. Chester S. Keefer.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, June 1, at 7:15 p.m. in the classroom in the nurses' residence. Dr. Samuel R. Meaker will speak on the subject, "Sterility." Dr. Ilia Galleani will be chairman.

(Continued on page xv)

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THIOURACIL IN THE TREATMENT OF THYROTOXICOSIS*

A Report of Seventy-Two Cases

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BOSTON

IN THYROTOXIC patients thiouracil has been found to cause a lowering of the metabolic rate to normal levels, a return to normal of the protein-bound iodine of the plasma and concurrently a clinical remission of the disease.^{1,2} The evidence accumulated suggests that these changes result from the action of the drug on the thyroid gland, decreasing in some manner the formation of its hormone. Since the appearance of the above reports we have used thiouracil§ in the treatment of 72 thyrotoxic patients, including a continuation of treatment of the 9 patients reported by Williams and Bissell.² In the course of these studies a number of observations were made concerning the progress of the disease as influenced by prolonged treatment with thiouracil, the desired dosage, the complications arising from the use of the drug, the use of thiouracil instead of iodide preoperatively and the production by thiouracil of certain anatomic and chemical changes in the thyroid gland.

The present series includes all the patients with thyrotoxicosis seen since the beginning of the study. A number of variations in the disease were found. There were examples of classic Graves's disease, toxic nodular goiter and toxic adenoma. The duration of the illness varied from three weeks to twenty-two years. Subtotal thyroidectomies had previously been performed on 13 patients. In one case this operation had been carried out three times, and in another twice. Thirteen patients had taken potassium iodide, for several weeks, discontinuing it within about a month before thiouracil therapy was begun. Most of the patients were not hospitalized for more than one day. Complete physical examinations were made, particular attention being

paid to the size, configuration and consistency of the thyroid gland and to the manifestations of exophthalmic ophthalmoplegia. Before the beginning of treatment an adequate number of determinations of the basal metabolic rate were made to indicate the degree of toxicity.

In the first 30 patients treated the initial daily dosage of thiouracil was usually 1 gm., but with subsequent patients it was 0.6 gm. daily or rarely 0.4 gm. In most cases, however, the dosage was reduced to 0.2 gm. daily over a period of about six weeks. Single doses usually consisted of 0.2 gm., although they were sometimes only 0.1 gm. When several doses were given daily, they were spaced evenly throughout the day for reasons that will be discussed later.

Almost all the patients were permitted to perform their usual duties but were asked to return to the outpatient clinic at the Boston City Hospital for observation, including a determination of the basal metabolic rate, at intervals of one or two weeks during the first six weeks of treatment, and at intervals of about four weeks thereafter. The white-cell count was usually made several times during the first six weeks, but thereafter only when the patient developed some type of infection or complained of vague weakness and malaise.

We have now treated 48 patients for more than two months, 35 for more than four months, and 16 for more than six months. Twenty-four patients have been treated for two months or less.

RESULTS OF TREATMENT

Although estimations of the clinical status of the patients were made at each visit, the thyrotoxicity can best be demonstrated by presenting the rates of basal oxygen consumption, since the results of this test were usually in accord with the observed clinical changes. Many patients maintained that a marked improvement had occurred within twenty-four to forty-eight hours after first taking thiouracil. This rapid change may have been due in part to a

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§Thiouracil was supplied through the courtesy of the Lederle Laboratories, Incorporated, Pearl River, New York.

mild sedative effect of the drug, as well as to its psychologic effects.

Changes in Basal Metabolic Rate

There were 59 patients who had not received iodide treatment for more than one month before thiouracil was started and were therefore probably free of iodide effect. These cases were divided into three groups according to whether the lowest metabolic rate preceding thiouracil treatment was from +55 to 89, from +35 to 55 or from +15 to 35 per cent; there were 16, 23 and 20 patients, respectively, in each division. For each group was calculated an average of the basal metabolic rates obtained before and after thiouracil treatment and at equal intervals thereafter. These results are plotted in Figures 1, 2 and 3, together with the extreme variations in the metabolic rates and the average

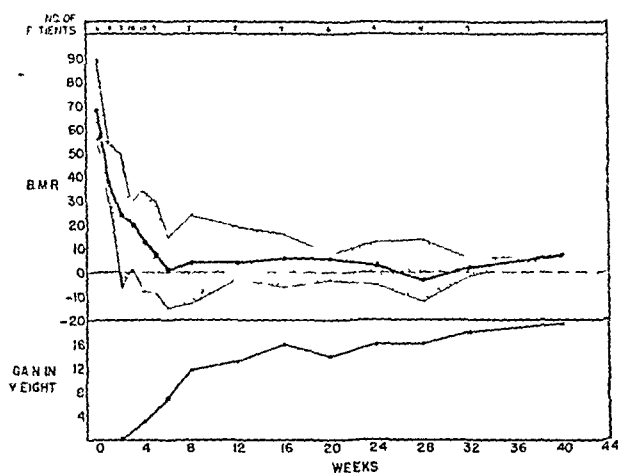


FIGURE 1. The Changes in Metabolic Rate and Weight in Association with the Thiouracil Treatment of 16 Patients with Marked Thyrotoxicosis.

weight gain. In these figures are included the results obtained preoperatively in 18 patients who had a subtotal thyroidectomy. One patient felt so well after a few months of treatment that he refused any more treatment or examination. Four patients discontinued therapy for intervals of two to four weeks, and 3 of these had a slight recurrence of their disease. All these patients had a normal basal metabolism for more than a month before discontinuing treatment. One patient discontinued therapy for three weeks after having taken it for two months, but there was no relapse. Therapy was resumed; a few months later she discontinued it for one month and experienced a recurrence of the disease, but there was no thyrotoxicity within three weeks after resuming treatment. Another patient discontinued therapy after three months and experienced a relapse in three weeks; complete remission did not occur until six weeks after resuming treatment. A third patient stopped taking the drug after seven months. An exacerbation was observed in two weeks, and the metabolic rate was not found

normal until four weeks after resuming treatment. The metabolic rates during the exacerbation in these 3 patients have been omitted, but those obtained after a few weeks of resumed treatment are included.

The basal metabolism decreased under thiouracil treatment much more rapidly in the severe cases

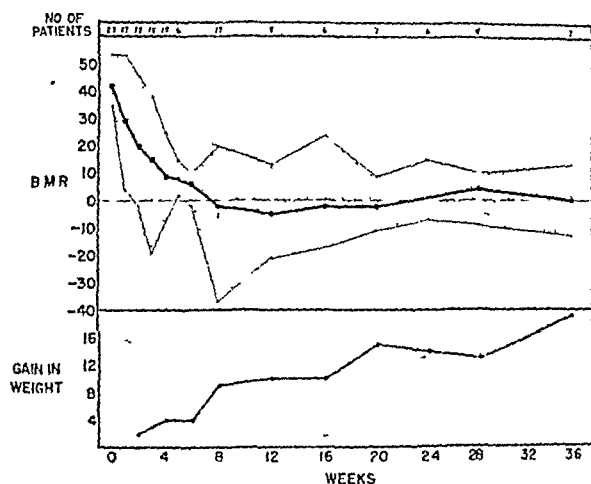


FIGURE 2. The Changes in Metabolic Rate and Weight in Association with the Thiouracil Treatment of 23 Patients with Moderately Severe Thyrotoxicosis.

(basal metabolic rate, +55 to 89 per cent) than in the others. It did not become normal on the average, however, until after five weeks of treatment, whereas in the moderately severe cases (basal metabolic rate, +35 to 55 per cent) this interval was four weeks, and in the mild cases (basal metabolic rate, +15 to 35 per cent) only three weeks. The basal metabolic rate had become normal in each patient within an interval of ten days to seven weeks. This statement does not apply to all the

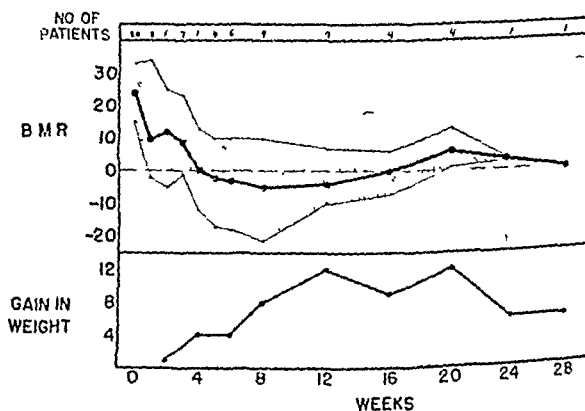


FIGURE 3. The Changes in Metabolic Rate and Weight in Association with the Thiouracil Treatment of 20 Patients with Mild Thyrotoxicosis.

cases subsequently operated on, because several of these patients were treated for less than two weeks. During the interval that they were observed, however, there was no difference in their response to therapy from that of the unoperated cases. In essentially all the patients the metabolic rate remained

normal following treatment, although occasionally a value slightly above normal was obtained that, on questioning the patient, was usually found to be related to excess work before the test, a respiratory infection or some other such extraneous factor. The slight tendency to a rise in the metabolism after about two months of treatment was probably related to reduction in dosage. In an attempt to use the minimal effective quantity of thiouracil the dosage was occasionally reduced to as little as 0.1 gm daily, which was sometimes inadequate. On the other hand, when the dosage was too large, the metabolic rate became undesirably low and the patient experienced distinct clinical manifestations of hypothyroidism. However, these changes could be rapidly altered by a slight readjustment in the dosage.

In most of the patients there was little or no gain in weight during the first two weeks of treatment. Indeed, in many cases there was an actual loss in weight. Gain in weight was rapid with four to eight weeks of treatment and gradually increased thereafter, occasionally becoming excessive.

There were 13 patients who received iodide therapy either within one month before commencing thiouracil or during its administration. Consequently, these cases are discussed separately from the foregoing 59. In Figure 4 are plotted the changes in the metabolic rate of these patients, each of whom had taken potassium iodide regularly for an interval of one month to two years, this therapy having been discontinued during a period of four weeks preceding thiouracil treatment; in this group a continued iodide effect was to be expected. At the time that the thiouracil therapy was begun the metabolic rate was normal in only one case. These patients tended to be resistant to thiouracil therapy, particularly during the first three weeks. In fact, in 3 of 5 cases in which there was an immediate transition from iodide to thiouracil therapy, a distinctly greater elevation in the metabolic rate was found two weeks later. Whereas a normal metabolism was ultimately obtained in the 5 patients treated for eight weeks or longer, this interval was distinctly longer than that required in the 59 cases previously discussed (Figs. 1, 2 and 3). This delayed response was observed even though no iodide had been given for as long as three weeks preceding thiouracil. The course of a tenth patient was apparently similar, but the data in this case are incomplete. The remaining 3 of the 13 patients received potassium iodide and thiouracil concomitantly. The response in two of these cases was about the same as one would expect from the use of thiouracil alone, whereas in the third case the metabolic rate declined very slowly; the latter patient had taken iodide for two years before beginning thiouracil treatment.

In 2 of the 59 patients already discussed, the changes in metabolic rate when the therapy was

changed from thiouracil to potassium iodide were also observed. In each case a slight exacerbation occurred.

Changes in Protein-Bound Iodine Content of Plasma

Although the accurate determination of the protein-bound iodine* content of the plasma represents one of the best methods of estimating the

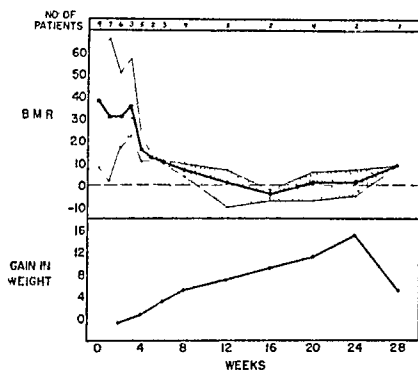


FIGURE 4. The Changes in Metabolic Rate and Weight in Association with the Treatment of 9 Patients with Thyrotoxicosis Who Had Previously Been Given Potassium Iodide. Note that the decrease in metabolic rate, as well as the gain in weight, took place more slowly than it did in those who had previously received no iodide therapy (Figs. 1, 2 and 3).

amount of thyroid hormone produced, the procedure involved is long and tedious and thereby tends to reduce extensive use. Nevertheless, in some cases the changes induced in this fraction by thiouracil therapy have been followed, the method of Riggs

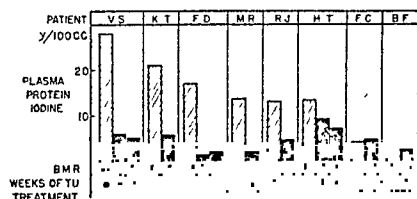


FIGURE 5. The Changes in the Concentration of the Protein-Bound Iodine of the Plasma Compared with those in the Basal Metabolic Rate following Thiouracil Treatment.

Patient F. C. had a colloid goiter, B. F. had myxedema, and the others had thyrotoxicosis. The dosage of thiouracil was, for the most part, 1 gm. daily.

and Man³ being used. The normal range is from 4 to 8 gammas per 100 cc. A few of the results have previously been reported.²

As shown in Figure 5, the protein-bound iodine returned to normal in each of the thyrotoxic patients in whom the determination was done. Indeed,

*The protein-bound iodine is composed of the so-called "D" and "T" iodines, which are essentially equivalent, respectively, to the di-iodotyrosine and the thyroxine content of the plasma.

in 2 subjects it reached the myxedema range. The data are sufficient to show that in at least 4 cases the iodine level became normal before the metabolic rate did. If this principle held in most cases, one would expect the plasma protein iodine to be normal in the majority of patients in about four weeks or less. The level was essentially normal in 2 cases within four weeks and in 2 others within two weeks. In 2 subjects estimations were made as long as twelve weeks after beginning thiouracil treatment, and in each case the iodine concentration was well within normal limits.

No change in the plasma protein iodine occurred in a patient with colloid goiter (F. C.) who was treated with 1 gm. of thiouracil daily for three weeks; nor did any definite change occur in a myxedematous subject (B. F.) similarly treated for two weeks.

One patient who stated that she had taken 15 drops of potassium iodide daily for two years had a basal metabolic rate of +44 per cent and a thyroxinlike iodine concentration in the plasma of 11.6 gammas per 100 cc. She was treated with 0.4 gm. of thiouracil daily. Five weeks later the basal metabolism was +15 per cent and the thyroxinlike iodine was 6.9 gammas per 100 cc. Thus, whereas this patient was not well controlled with iodide, she showed a distinct improvement when thiouracil therapy was given concomitantly with the iodide, although the response was slower than is generally the case when thiouracil alone is used.

Changes in Thyroid Gland

The changes in the size and consistence of the thyroid gland are difficult to discern. Nevertheless, attempts were made to evaluate these factors at each visit of the patient. An increase in the size of the gland was observed in 11 patients during the first few weeks of treatment with thiouracil. The consistence of these glands, as well as those of some other patients, became firmer soon after thiouracil was started. In 2 cases the thyroid gland was distinctly larger than it was cases no change In

In most of the patients, however, a distinct decrease in the size of the thyroid gland was observed after more than six weeks of treatment with thiouracil, and in 21 cases there was a 33 to 66 per cent decrease. In a few cases glands that were formerly two to three times normal size and of firm consistence returned to an essentially normal state. In

desiccated thyroid was used for several weeks in doses of 0.5 to 1.5 gr. daily to reduce the size of the thyroid gland. In most of the cases such treatment proved to be of advantage.

Ocular Changes

Five patients initially exhibited changes in the orbits characteristic of those found with malignant

exophthalmos.⁴ In each case the manifestations became worse during the first few weeks of treatment with thiouracil, and in 1 case they became severe, the patient developing marked palpebral edema, conjunctival injection and chemosis, marked lacrimation and several corneal ulcers. Desiccated thyroid was used in the treatment of these subjects after the metabolic rate had become normal under thiouracil therapy. The rationale of this treatment will be discussed later.

All the patients who exhibited a stare and widened palpebral fissures experienced a distinct improvement in these disturbances as the metabolism became normal. Many patients stated that their eyes were "looking normal again."

Complications

The most serious complication encountered was leukopenia with agranulocytosis, which was experienced by 1 patient. This was discovered at the end of six weeks of treatment, during which the patient received 0.6 gm. of thiouracil daily for the first two weeks, 0.4 gm. daily for the next two weeks and 0.2 gm. daily for the last two weeks. A white-cell count was made when the patient complained of fever and an infected finger. She was treated with Pentnucleotide and large doses of crude liver extract. Complete recovery resulted, although only a few granulocytes were present for a period of seven days. In another case the white-cell count dropped to 3200, with 20 per cent granulocytes; only a few days after beginning thiouracil treatment. In spite of continued therapy, however, the white-cell count returned to normal and the granulocytes increased to 50 per cent. Subsequently, the patient took thiouracil for more than six months and remained in good health. Leukopenia and granulocytopenia were seen in some other cases, but the incidence was apparently no greater than that observed in untreated thyrotoxic patients.¹⁷ Four patients developed a morbilliform rash associated with itching, but this disappeared in spite of continued treatment. Three others developed moderately severe urticaria. One of these patients discontinued thiouracil for three days and then resumed it without recurrence. Another with urticaria developed painful swollen and stiff joints lasting one week. Following this episode iodide therapy was substituted. The third patient developed urticaria and fever after eight months of thiouracil therapy and a thyroidectomy was then performed. Six patients developed swelling of the legs that was not associated with hypoproteinemias, cardiac failure or evidence of renal damage, but data obtained from some of these patients, as well as others, indicate that thiouracil in certain dosages may cause a retention of sodium, chloride and water. A decrease in the carbon dioxide combining power of the blood was also found in a few of these patients, but

these changes disappeared in spite of continued therapy.

Two patients experienced nausea and vomiting during the first week of treatment, but these symptoms disappeared without stopping of the medication. Another patient had swelling and soreness of

of whom had received thiouracil preoperatively in amounts and for periods of time designated in Table I. The colloid goiters were removed chiefly because of their large size, as was the case in 4 thyrotoxic cases. In 6 cases the gland was removed because the patient desired this treatment at the

TABLE I Data in Cases With Thyroidectomy.

NAME	THIOURACIL TREATMENT		CLINICAL DATA DURING OPERATION				WEIGHT OF THYROID GLAND		DRY WEIGHT CONTENT OF THIOURACIL		REMARKS
	DURATION BEFORE OPERATION	DAILY DOSAGE BEFORE OPERATION	Maximal Pulse Rate	Maximal Blood Pressure	Maximal Pulse Rate	Maximal Temperature	gm	mg/100 gm	ENTIRE GLAND	COLLOID	
	days	gm		mm Hg		°F			mg/100 gm		
TOXIC GOITER											
HA	8	0.6	150	165/95	125	100.5	23	12			
JB	35	0.4	90	180/120	88	101	14				
BJ	1	1.0	105	160/80	100	99.5	14	14			Preoperative treatment consisted of potassium iodide thiouracil given on day preceding operation
EH	47	0.1	130	170/100	100	101	500	22	25		Desiccated thyroid, 1 gr daily for first 30 days of thiouracil treatment
MA	37	0.4	120	165/110	96	99.8	39	5			Desiccated thyroid, 0.5 gr daily, for first 23 days of thiouracil treatment
HO	90	0.6	125	200/110	100	100	29	23			
WO	19	0.4	90	160/70	90	102	35	39			
LA	26	0.6	140	220/90	140	101	76	8			Potassium iodide for 6 weeks, ending 10 days before operation
DE	68	0.6	110	190/110	100	100	59	14			
IT	30	0.3	130	145/90	105	101.5	32				
BA	27	0.4	150	170/110	105	100	20	9			
	12	0.6	120	150/75	110	100.5	22	15			Potassium iodide for 2 months, ending 3 weeks before beginning of thiouracil treatment
GA	32	0.4	100	160/100	128	100	44	18	60		Potassium iodide for 4 months ending 2 weeks before thiouracil treatment
BO	9	0.4	145	180/70	130	101.5	50	6			
CO	19	0.4	110	170/100	120	101.5	20	8			Potassium iodide for 1½ days before operation
MU	22	0.4	115	105/80	95	101	9	28			Potassium iodide, as well as thiouracil, for 1½ days before operation
SL	23	0.4	110	140/70	95	101.5	21	20	68		Potassium iodide, as well as thiouracil, for 1 day before operation
MC	23	0.4	160	195/130	135	99	61	19	41		
AO	13	0.6	110	150/80	120	100	23	21	31		Potassium iodide, as well as thiouracil for 14 days before operation
RO	24	0.6	105	140/80	100	100	40	12	49		Thiouracil for 5 days beginning 17 days before operation, potassium iodide for 9 preoperative days
MN	5	0.6	180	185/120	128	101	14	0			No thiouracil for 7 days before operation
TR	240	0	155	165/100	110	101	42	14			Potassium iodide for 2 months, ending 5 weeks before thiouracil treatment
LO	8	0.6	80	190/95	108	101.5	14	17			
COLLOID GOITER											
PO	4	0.6	100	125/80	105	100	8	8			
MG	9	0.6	130	220/125	120	101	255	28			Potassium iodide 1 day before operation
GR	11	0.6	90	225/135	100	101	150	12			

the submaxillary salivary glands, which subsided without alteration of the treatment.

In summary, untoward reactions of some sort, ranging from mild to severe, occurred in 13 of the 72 patients treated. In only 3 were these reactions of such severity as to necessitate discontinuation of the drug, although in some cases therapy was omitted until the symptoms ceased.

THYROIDECTOMY FOLLOWING THIOURACIL TREATMENT

A thyroidectomy was performed on 22 thyrotoxic patients and on 3 patients with colloid goiters, each

outset. In 11 cases it was removed because such factors as distant residence or business obligations interfered with adequate observations. The gland was removed from 1 patient after she had developed urticaria that was apparently due to thiouracil. However, in no case was a thyroidectomy performed because of any evidence that the metabolic rate could not return to normal with the use of thiouracil alone. In fact, in 13 of these 22 patients the basal metabolism was normal at the time of the operation. Eight of the other 9 patients had received treatment for less than four weeks, but during this interval they showed the usual lowering of the basal

metabolic rate that occurred in the nonoperated group. The remaining patient had a basal metabolism of +17 per cent at the time of operation, having received thiouracil for five weeks. Judging from the course of other cases, however, the rate would most likely have been normal within another week.

The actual duration of thiouracil treatment preceding operation varied from one day to two hundred

99 to 102°F., averaging 100.7°F. The postoperative period of hospitalization varied from five to fifteen days, averaging eight days. On the whole, the course of the patients during and following the operation was relatively smooth in all but 3 cases, these patients being excited and restless. In none of the latter cases had thiouracil been given for as long as ten days. In general, the patients treated with thiouracil and without iodine for as long as



FIGURE 6. Section of Thyroid Gland of a Thyrotoxic Patient Treated with Thiouracil for Twenty-Three Days.

Note the scanty colloid and the great mass of cells. Most of the colloid is quite pale, although a few deep-staining clumps are seen in the right lower corner. The cells are hyperplastic, and the lumens of many acini are largely obliterated. Increased interstitial tissue is observed in some areas.

and forty days, and the daily dosage was usually 0.4 or 0.6 gm. Some of the patients had iodine therapy either before, during or after the thiouracil therapy, as noted in Table 1. One patient was operated on in two stages under cyclopropane and ether anesthesia. There were no greater technical difficulties in the removal of the gland after thiouracil therapy than exist after iodide therapy, except for slightly more vascularity and friability of the tissue. The maximal pulse rate during the operation varied from 80 to 180, averaging 123. In 16 subjects it never exceeded 130. The highest systolic blood pressure varied from 135 to 220, averaging 169, and the highest diastolic pressure varied from 70 to 130, averaging 95. Of course, almost throughout the operation in each case the pulse rate and blood pressure remained at distinctly lower levels than indicated above. The maximal pulse rate following the operation varied from 88 to 140, averaging 110, and the maximal temperature ranged from

three or four weeks had an extremely smooth course.

It is much too early to evaluate the results of operation, although with the short periods of observation made thus far there has been no evidence of persistence or recurrence of toxicity.

ANATOMIC AND CHEMICAL CHANGES IN THYROID GLAND

Anatomic Changes

The thyroid glands of patients who received thiouracil for more than two weeks were distinctly firmer than normal, having a rubbery consistence. The cut surface was uniformly grayish-yellow, with a slightly pink hue. Many of the glands had little visible colloid and were more friable than normal. On microscopic examination a moderate variation in the structure of the gland was found. In the group of patients who received no iodide at any time but were treated with thiouracil for intervals of

eight to thirty-two days, it was found in general that the longer the drug had been given the greater the thiouracil effect (Fig. 6). Glands showing this effect to a pronounced degree possessed many or all the following characteristics. A marked scarcity of colloid was readily noted, the tissue consisting of an almost solid sheet of cells in many areas. The colloid that was present tended to be quite pale. Many acini appeared small and contracted, the lumen having almost entirely disappeared. On the other hand, a few acini had an enlarged lumen and these were apt to show papillary projections. The cells were tall and columnar. There was an increase in the interstitial tissue, with a noticeable increase in fibroblasts, lymphocytes and collagen. In some areas there were foci of dense lymphocytic infiltration ramifying between the acini in a disorderly manner, but it was commoner to observe well-circumscribed lymph follicles, many with prominent germinal centers, consisting of lymphoblasts in the center with a few clumps of collagen and an occasional macrophage, all densely surrounded by lymphocytes. These lymph follicles were usually subcapsular. They were present in about half the cases, and were larger and more prominent than the occasional cluster of lymphocytes commonly seen in the thyroid gland.

Changes were seen varying in degree from the ones described above to those of an untreated thyrotoxic gland. In no case, however, was there anything resembling the appearance of iodized glands. There was no striking difference in the appearance of the glands of the 2 patients treated for three months and eight months, respectively, from that of the glands of certain patients treated for only one month.

It was of interest to note that in a case treated with thiouracil for twenty-four days, during the last fourteen days of which potassium iodide was also given, the gland showed a classic iodine effect with no evidence of a thiouracil effect. A patient who also took thiouracil for five days, nothing for the next three days and then potassium iodide for the next nine days was found to have no definite iodine effect in the thyroid, the gland appearing like an untreated thyrotoxic gland with perhaps a slight thiouracil effect.

One patient was given iodide for six weeks, during the last nine days of which thiouracil was given. The latter drug was continued until a hemithyroidectomy was performed seventeen days later. The gland showed a large amount of moderately deep-stained colloid and slight hyperplasia of the acinar cells. Thiouracil treatment was continued, and forty-two days later a second operation was performed. The tissue removed at this operation showed less colloid but more hyperplasia than did the portion removed at the first one. It seems probable that the iodide therapy influenced the effects of thiouracil long after the former had been dis-

continued. Two other patients exhibited this same phenomenon to some extent.

Changes in Concentration of Thyroxin Iodine

In 11 thyrotoxic cases about two thirds of each thyroid gland was analyzed for its thyroxin iodine content by the method of Leland and Foster.⁶ The results were compared with those given by Gutman, Benedict, Baxter and Palmer⁷ for normal glands, iodized exophthalmic glands and noniodized exophthalmic glands. The glands of 7 patients treated with thiouracil and no iodide had distinctly less thyroxin iodine than did those of patients who received no treatment (Fig. 7). There was an ex-

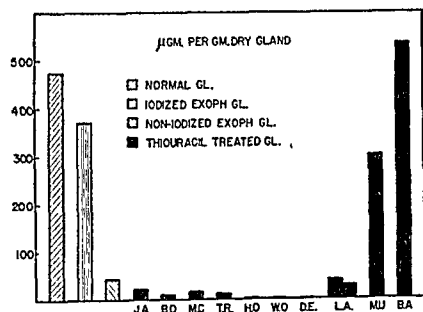


FIGURE 7. Thyroxin Iodine in Thyroid Glands (micrograms per gram dry tissue).

The average values for the normal glands and for the iodized exophthalmic glands were taken from Gutman and his co-workers,⁷ and the average value for the noniodized exophthalmic glands was calculated by these authors from the data of Wilson and Kendall.⁸ Patients B. O., L. A., and B. A. had had some iodide therapy before thiouracil treatment was begun. The results of a two-stage operation are given for patient L. A. Patient M. U. had no iodide until a day and a half before thyroidectomy, a relatively high concentration of thyroxin iodine was present. Note especially the small concentration of thyroxin iodine in the glands of patients treated with thiouracil and no iodide.

Extremely small amount of thyroxin iodine in the thiouracil-treated glands, as compared with the quantity in normal or iodized exophthalmic glands. Of the 4 patients who had received iodide therapy, one patient (B. A.) had a large amount of thyroxin iodine in the gland although she had had no iodide for five weeks. On the other hand, another patient (B. O.) with a similar schedule of treatment had less thyroxin iodine than the average amount in nontreated exophthalmic glands. One patient (M. U.) who had never had iodide treatment except for the day and a half preceding operation had a relatively large concentration of thyroxin iodine in her gland. The fourth subject (L. A.), who was treated with iodide for six weeks, ending ten days before hemithyroidectomy, had essentially the same concentration of thyroxin iodine as in the average untreated exophthalmic gland. Although

after forty-two days of additional thiouracil treatment the amount of iodine in the second half of the gland had decreased, it was still larger than that found in the glands of patients who had received thiouracil and no iodide.

Concentration of Thiouracil

Immediately after removal of the thyroid gland an analysis was begun to determine the concentration of thiouracil therein, using the method of Williams, Jandorf and Kay.⁹ In the patients who had continued thiouracil therapy until the day of operation, the values ranged from 5 to 39 mg. per 100 gm. of dried gland. A patient (T. R.) who had had no treatment for seven days preoperatively was found to have 14 mg. per cent. Patients treated for as long as fifteen days tended to have as great a concentration as did those treated for longer intervals. Previous iodide therapy had no effect on the amount of thiouracil present, but 3 patients treated with thiouracil alone and then given iodide therapy during the day preceding operation obtained a higher average level than did the other patients. The variations in thiouracil concentration were not associated with any consistent alterations in histologic structure. Furthermore, they did not correlate with the concentrations of thyroxin iodine in the thyroid gland or with the clinical response.

An effort was made to ascertain whether thiouracil was stored equally in the colloid and in the parenchyma. In 6 cases, a portion of the gland was sectioned into several large pieces and these were gently squeezed by a metal compressor. By this procedure, which is admittedly crude, it was hoped to express some colloid and not many cells or tissue fluid. The fluid so obtained in the 6 cases contained a concentration of thiouracil distinctly greater than that of the whole gland, when expressed in terms of dry weight (Table 1). Two glands were given a second and a much firmer compression with the hope of obtaining a moderate amount of tissue fluid. This fluid and the residual tissue were separately analyzed for the concentration of thiouracil. The tissue fluid had a higher concentration of thiouracil than did the residual tissue (Table 2). When the quantity of thiouracil was ex-

The problem of the distribution of thiouracil between colloid and cells was also approached by comparing its concentration in glands containing little colloid with that in those containing moderate amounts. No significant differences were found.

DISCUSSION

The experiences reported here in the treatment of thyrotoxicosis with thiouracil indicate that this drug can be depended on in essentially all cases to lower the basal metabolic rate to a normal range and to maintain it at that level so long as treatment is continued. Associated with this response in the basal metabolic rate is a clinical remission of the disease, with disappearance of tachycardia, hyperidrosis, nervousness, diarrhea, weight loss and other toxic manifestations.

Thiouracil causes a decrease in the protein-bound iodine of the blood and in the thyroxin iodine of the thyroid gland, but does not inhibit the hypermetabolic effects of preformed thyroxin.² These facts indicate that thiouracil inhibits the production of the thyroid hormone, but the exact process by which this is accomplished has not yet been determined. Presumably, when the production of the thyroid hormone is markedly inhibited, there results an excessive production of thyrotropic hormone, which in turn causes hyperplasia of the acinar cells of the thyroid and certain manifestations of malignant exophthalmos.⁴ Thus, as we have observed in several cases, with the use of thiouracil in excessive quantities in thyrotoxic patients a still greater enlargement of the thyroid gland may result and the manifestations of malignant exophthalmos may be accentuated. Under such circumstances it is advisable to reduce the dosage of thiouracil. In some cases, however, the use of desiccated thyroid also seems indicated, since it not only inhibits the production of thyrotropic hormone but also exerts a diuretic effect that is of advantage in the control of the severe cases of malignant exophthalmos. To be sure, on theoretical grounds one may argue that the same thing can be accomplished by permitting the patient's own thyroid gland to manufacture more hormone. Nevertheless, we have thus far had better success by decreasing the thiouracil to a sufficiently small dosage to maintain a normal metabolic rate and then giving 1 to 1.5 gr. of desiccated thyroid daily. Before adopting this policy, however, we first sought to discover whether thiouracil would inhibit the inactivation of administered thyroid, it having been shown¹⁰ that persons with normal thyroid glands can inactivate large quantities of desiccated thyroid or thyroxin.

To elucidate this problem 3 patients were treated with relatively large doses of desiccated thyroid for intervals of thirty to fifty days, during the last two or three weeks of which 0.6 gm. of thiouracil was administered daily. No significant changes in the basal metabolic rate occurred in any of these pa-

TABLE 2. Distribution of Thiouracil in the Thyroid Gland.

NAME	SPECIMEN	CONTENT OF	CONTENT OF THIOURACIL	
		WATER	DRY WEIGHT	WET WEIGHT
		%	mg./100 gm.	mg./100 gm.
M.C.	Whole gland	80	19	4
	Colloid	88	41	5
	Tissue fluid	86	39	5
	Residue	77	18	4
K.O.	Whole gland	77	21	5
	Colloid	80	31	6
	Tissue fluid	76	16	4
	Residue	74	12	3

pressed in terms of wet weight there was only a slightly greater concentration in the colloid than was present in the gland as a whole.

tients (Fig. 8). Furthermore, the thyroxine-like iodine of the plasma, determined in 1 case (D. U.) actually decreased following the thiouracil treatment.

Clinical studies were also conducted that indicated that thiouracil can inhibit the effect of relatively large amounts of thyrotropic hormone in increasing the production of thyroid hormone. Williams and Bissell² found that when 1 gm. of

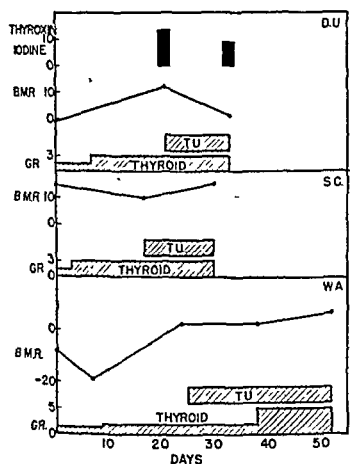


FIGURE 8. Basal Metabolic Rates in 3 Patients without Thyroid Disease Treated Simultaneously with Thiouracil and Desiccated Thyroid.

Note that no significant change in the basal metabolic rate resulted from large doses of desiccated thyroid whether or not thiouracil (0.6 gm. daily) was also given. A slight decrease in the thyroxine iodine (expressed in micrograms per 100 cc) of the plasma resulted in one case (Patient D. U.)

thiouracil was given daily with 2 cc. of thyrotropic hormone (Antuitrin T) in sesame oil to a normal subject for a period of ten days, no elevation in the basal metabolism resulted, although a goitrogenic effect was noted. Subsequent unpublished studies showed that no change results in the concentration of the protein-bound iodine of the plasma. This experiment was repeated in another normal subject using the same amount of thyrotropic hormone for eight days but no thiouracil. Although no significant elevation in the metabolic rate occurred, the plasma iodine showed a marked rise, increasing from 8 to 15 gammas per 100 cc. Thus, the marked inhibitory effect of thiouracil in the first case is apparent.

In choosing the ideal dosage of thiouracil it is desirable to use the smallest amount necessary to obtain a remission of the disease, but it has been found that this quantity varies with different patients. In an attempt to establish an objective method of ascertaining this dosage, Williams, Kay

and Jandorf¹¹ determined in a large number of cases the concentration of thiouracil in the blood when the patient was given from 0.2 to 1.2 gm. daily. The blood level remained relatively constant, regardless of what dose was given. Furthermore, using the above range of doses we have found no directly proportional concentration of the drug in the thyroid gland. In the course of varying the dosage, however, the amount of drug necessary to obtain an adequate response in thyrotoxicity was distinctly less than the amount that was first used.^{11, 12} An outline of treatment with thiouracil that we have found extremely satisfactory is the following: 0.2 gm. three times daily for the first two weeks, followed by 0.2 gm. twice daily until the metabolism is normal and then 0.1 gm. twice daily until the basal rate has been maintained well within normal limits for several weeks, when the dosage can be reduced to 0.1 gm. daily. Cases have rarely been encountered in which larger doses were necessary, and in a number of cases smaller ones were used. Whatever schedule of dosage is to be used, it should be borne in mind that thiouracil is rapidly absorbed and excreted.¹¹ Thus, it is better to give two or three decreased doses per day than it is to give only one. On the other hand, the prescription of many small doses may cause the patient to become quite irregular in taking treatment.

Williams, Kay and Jandorf¹¹ found that the routine estimation of the thiouracil content of the blood and urine was of no definite aid in treatment. Most of the tissues of the body can break down large amounts of thiouracil, thereby interfering with its accumulation in the blood of normal subjects as well as of patients with severe disease of the heart, kidneys or liver.

Of the various complications thus far encountered, the only one to cause appreciable concern is agranulocytosis. Patients who develop urticaria or any other allergic manifestation, however, should be carefully observed when treatment is resumed, since other sensitivity phenomena may result.

Much more must be learned before the role of thiouracil in the medical treatment of thyrotoxicosis can be fully evaluated. In most cases its great dependability in controlling the toxicity makes hospitalization unnecessary. Furthermore, the majority of patients can continue regularly with their work. Nevertheless, patients treated in this manner should maintain close contact with the physician, particularly during the first two months. How many patients can discontinue therapy without a relapse in the disease remains to be demonstrated. The prolonged course of treatment does not of itself constitute much of a burden, since the maintenance dosage does not have to be varied much once it has been properly estimated. The possibility of chronic complications and the development of therapeutic unresponsiveness to the drug must be borne in mind, although we have thus far seen no evidence.

By accurately regulating the dosage of thiouracil it is believed that the goitrogenic effect can be kept low. In fact, in most cases the gland tends to decrease in size. Two reasons for this decrease may be advanced: a marked decrease in the content of colloid, permitting a collapse of the acini, and an exhaustive phenomenon — an atrophy of the cells resulting from the prolonged stimulation by the thyrotropic hormone. The first phenomenon was often observed in our patients, but no evidence of the second has yet appeared.

In spite of the fact that many thyroid glands have decreased in size with treatment, it is not considered advisable to give prolonged thiouracil treatment to a patient who has an extremely large gland, since there is some possibility that the gland will actually become larger. Since some of these patients have compression of the surrounding structures, the risk of further trouble should not be taken. However, the drug has been used preoperatively in some patients with extremely large glands. In fact, the gland of one patient weighed 500 gm. at operation in spite of a decrease in the neck circumference of 2.5 cm. during treatment. In this case, as in somewhat similar ones, desiccated thyroid was used with the thiouracil.

Thus far, we have not found that iodide used preceding or during thiouracil treatment is of any advantage. In fact, the patients who had iodide previously responded more slowly to thiouracil than did those who had not had any. Furthermore, in some cases there was actually an exacerbation of the disease if thiouracil was suddenly exchanged for iodide. This is to be expected when one considers that iodide causes storage of the hormone in the thyroid gland, whereas thiouracil apparently does not possess this action and thereby permits escape of the stored hormone into the blood stream. Bearing these phenomena in mind, when our patients are changed from iodide to thiouracil therapy, the treatments are overlapped for about two weeks, the amount of iodide therapy during this interval being progressively decreased.

There is evidence from studies in guinea pigs that the simultaneous administration of potassium iodide and thiouracil causes a greater concentration of the latter in the thyroid gland than occurs when the iodide is omitted.¹² On the other hand, in rats after thiouracil has been given for several days the uptake of radioactive iodine in the thyroid gland is decreased.¹³ Nevertheless, in a patient who was treated with thiouracil for three weeks and given iodide for 1.5 days preoperatively, a distinctly greater quantity of thyroxine iodine was found in the thyroid gland than in cases treated similarly with thiouracil without iodide.

The use of thiouracil in preoperative preparation has the advantage over iodine of dependability in causing a disappearance of the toxic manifestations of the disease in essentially every case, provided

that the treatment is continued for several weeks. Because of this dependability the patient may be permitted, in most cases, to perform a part or all of his usual activities during the period of preparation for the operation. Of course, during this interval adequate rest and a high-caloric diet supplemented by moderate amounts of vitamins, particularly thiamine and the members of the vitamin B complex, are desirable. A period of preparation of four to five weeks has thus far proved satisfactory. Since thiouracil decreases the quantity of thyroxine in the thyroid gland, in cases treated with this drug there is potentially less thyroxine to get into the blood stream at the time of operation than in the cases treated with potassium iodide.

SUMMARY

The results of treatment with thiouracil of 72 thyrotoxic patients are given.

The subjects who had not had iodide therapy for one month or more (59 cases) were arbitrarily divided into three classes according to the height of the basal metabolic rate preceding treatment. The decline in the basal rate was more rapid in the severe cases (basal metabolic rate, +55 to 89 per cent) than in the others, but required an average of five weeks to become normal, whereas in the moderately severe cases (basal metabolic rate, +35 to 55 per cent) only four weeks was necessary, and in the mild ones (basal metabolic rate, +15 to 35 per cent) only three weeks. The lowering of the basal metabolic rate in patients who had taken iodide until the thiouracil treatment was started was slower. All patients, however, regardless of the type of thyrotoxicity or of previous treatment, eventually attained a normal metabolic rate and a remission of the disorder.

Thirty-five patients were treated with thiouracil for more than four months and 16 for more than six months. Essentially all patients maintained a normal basal metabolism. In 4 patients who discontinued therapy after a few months, a relapse occurred in about three weeks, but a remission was again obtained with thiouracil treatment.

In the few cases where the plasma protein iodine content was determined this value became normal and tended to do so before the metabolic rate became normal. Although a transient increase in the size of the thyroid gland occurred in several cases, in the majority an ultimate decrease in the size of the gland resulted, this change being marked in some subjects. A few patients with malignant exophthalmos experienced an exacerbation in this process under thiouracil therapy, but with a decrease in the dosage of thiouracil and the use of desiccated thyroid an improvement resulted.

One patient developed agranulocytosis; other complications consisted of morbilliform rash, urticaria, allergic arthritis, edema of the legs, vomiting and enlargement of the submaxillary salivary glands

Although many estimations were made of the content of thiouracil in the blood and urine, these determinations are not necessary, since with the range of dosage employed the drug has not been found to accumulate appreciably in the blood, in spite of the presence of severe disease of the kidneys and liver.

For reasons other than an unsatisfactory response in the toxic manifestations of the disease 22 patients were subjected to thyroidectomy. The operative and postoperative course was relatively smooth, particularly in the patients treated with thiouracil for three weeks or longer preceding operation. A chemical analysis of these glands for the concentration of thiouracil showed a great variation in the amount of drug present. With these cases there was no correlation of the therapeutic response with the level of the drug in the gland. The thyroxine iodine was found to be extremely low in most of the glands that were analyzed. The pathologic alterations in the thyroid gland resulting from thiouracil treatment are described; they are quite unlike the changes found after iodide therapy.

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Mankowich and W. A. Dafoc, for clinical assistance, and to the Misses J. B. Peters and G. A. Kay for the chemical determinations.

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FAVUS IN MASSACHUSETTS*

A Report of Two Cases

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FAVUS is a rare fungus infection, and only a few cases of it have been reported from Massachusetts. Search of the records of the Boston City Hospital revealed that no cases had been seen there during the last ten years. This report of 2 cases is of interest, first because of the rarity of the disease, and second because of the satisfactory response to therapy.

The disease is usually caused by *Achorion schönleini*, but on rare occasions *A. quinckeanum* has proved to be the etiologic agent. The fungus may be found in or on the hairs, in the scutula and in and on the skin and nails. Microscopically the hairs, when softened in 30 per cent potassium hydroxide solution, show a characteristic diagnostic picture. They are usually covered with air bubbles, which are thought to be the result of displacement of air in the dead fungic filaments by the potassium hydroxide solution. On the outside, both spores and filamentous forms occur; within the hairs, coarse mycelial threads, usually broken into oblong bars

and into chains of spores (arthrospores), are found running parallel to the long axis of the hairs. These intrapilar filaments and spores are coarser and fewer than are those seen in Trichophyton infections, and favus spores are two to three times larger than are the spores seen in Microsporon infections (Fig. 1).

The scutula, which may be found on the scalp or glabrous skin, comprise almost pure cultures of the organism. Achorion is the only pathogenic fungus that grows on the skin in such pure form.¹

On Sabouraud's medium, the organism grows slowly to form a discoid, smooth, waxy or semi-translucent, convoluted, yellowish-brown colony that frequently grows deeply into the medium, causing large fissures to occur in it. Microscopically the culture shows coarse, septate and branched filaments with numerous chlamydoconidia, arthrospores, terminal clubs and favic "chandeliers" (Fig. 2).

CASE REPORTS

CASE 1. E. S., an 18-year-old girl of Jewish parentage, was first seen at the Out-Patient Department of the Boston City Hospital in August, 1941, complaining of a rash on the scalp of 2 years' duration. This had started as a small spot of baldness and had enlarged despite various local applica-

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tions prescribed by several physicians. The parents were born in Lithuania and had come to America 9 years prior to the birth of the patient. The latter was born in Pennsylvania and had lived there during the first 14 years of life, after which the family moved to Massachusetts.

Physical examination revealed an irregularly rounded area of patchy alopecia approximately 10 cm. in diameter over the vertex of the scalp. Many of the hairs in this area were

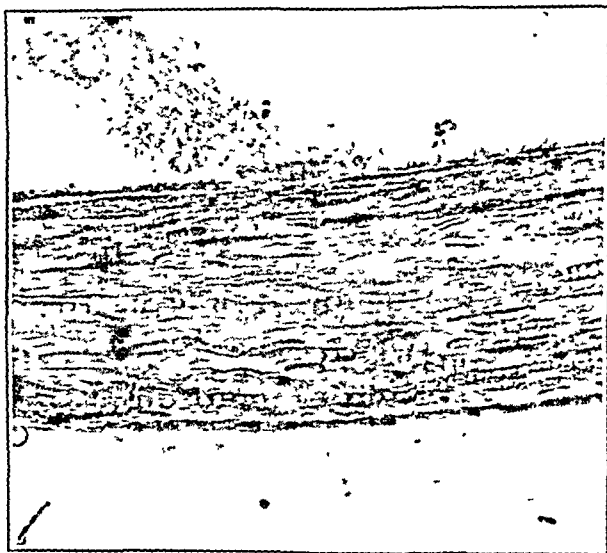


FIGURE 1. Hair in Potassium Hydroxide Solution, Showing Chains of Spores within the Hair.

dull and bent at acute angles, and some were broken off about 2 cm. from the scalp. There were several sulfur-yellow scutula, each pierced by a hair, adhering to the skin, which showed areas of atrophy and scarring. Examination of the scalp under a Wood's filter* revealed the yellowish-green fluorescence that is characteristic of hairs infected with *Achorion*.

Microscopic examination of hairs softened with potassium hydroxide solution revealed the characteristic picture of favus, and subsequent culture showed the presence of *A. schönleinii*.

Examination of the other members of the family revealed no evidence of active or healed infection with *Achorion*.

CASE 2. J. C., a 17-year-old girl of Italian parentage, entered the Out-Patient Department of the Boston City Hospital in July, 1942, complaining of a "rash" of the scalp of 4 years' duration, which had steadily progressed despite numerous forms of local therapy. The patient was born in Massachusetts and had never been outside the Commonwealth. Her father and mother had migrated from Italy 7 years prior to her birth.

Physical examination revealed three irregularly rounded areas of patchy alopecia involving almost the entire vertex of the scalp. The hairs of these areas were lusterless, thickened and fragile. Many were broken off close to the skin, which was studded with sulfur-yellow scutula and crusts. There were areas of scarring and atrophy of the underlying epidermis. The left leg, close to the knee, showed a single rounded, sulfur-yellow scutulum, 8 mm. in diameter, adhering to the skin.

The infected hairs showed the characteristic greenish-yellow fluorescence under the Wood's filter. *A. schönleinii* was cultured from the scalp and from the scutulum on the leg.

Examination of the other members of the family revealed no evidence of active or healed infection with *Achorion*.

*The Wood's filter is obtained by passing ordinary ultraviolet light from a mercury-vapor or carbon-arc lamp through glass that is so constructed that it absorbs all visible light (wave lengths 0.4100 to 0.7600 microns) but passes wave lengths between 0.3100 and 0.4100 microns. The best glass for dermatologic use is one whose maximum transmission lies between 0.3600 and 0.3700 microns. Such a piece of glass, suitably cut, may be fitted into a light-impermeable cloth hood, which is placed over the source of the ultraviolet light. Examination is carried out in a dark room. Such a filter permits easy identification of hairs infected with fungi.

Therapy of favus of the scalp is notoriously difficult. Sutton and Sutton² state that x-ray therapy constitutes the most reliable and efficient remedy, and Ormsby and Montgomery³ assert that such therapy offers the best method of treatment, without which months and years are consumed in effecting relief. Despite the opinion of these and other authorities, x-ray epilation is not a universally successful method of treatment; for Muskatblit⁴ treated 3 cases of favus in this manner, with recurrence of the infection in all of them. A fourth case was treated with thallium by mouth. Successful epilation of the hairs followed this medication, but recurrence of the favus also occurred in this case. Muskatblit states that in his experience recurrence is common after such epilatory procedures.

Similar failure of roentgen-ray epilation to cure a patient previously under my care led to an extensive search for other more effective methods of therapy.

Trained mycologists are aware that cultures of various fungi may be killed by applying a few drops of formalin to the cotton stoppers of the tubes. The formalin decolorizes the fungi, so that the killed culture loses the characteristic and often diagnostic pigmentation of the living organisms and, incidentally, makes it valueless for teaching purposes. Such a solution, however, cannot be safely applied to the skin, for the aldehydes are well-known skin sensitizers and irritants.⁵ I found that a solution of 10 per cent thymol in chloroform would kill but

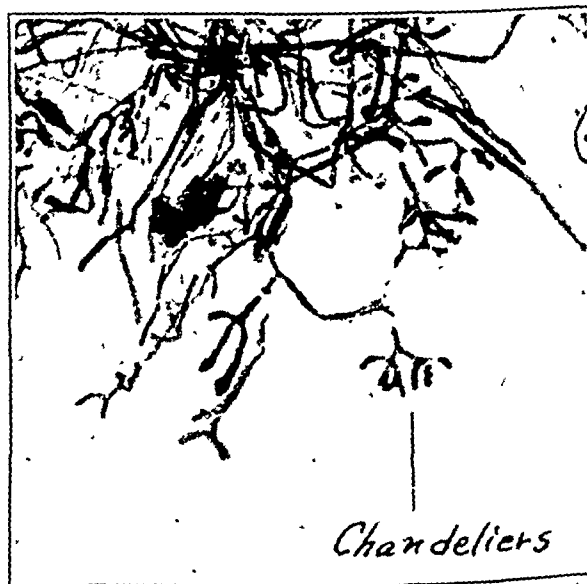


FIGURE 2. Stained Culture of *Achorion schönleinii*, Showing Segmented Filaments, Terminal Clubs and Favic "Chandeliers."

not decolorize cultures of fungi. Since thymol does not sensitize and irritate the skin as does formalin, it was used as a therapeutic agent in these cases, being applied twice daily to the affected parts.

The patients were advised to shampoo the scalp twice weekly, and for the first three months used

the above prescription exclusively. They were instructed to epilate the hairs manually from the affected parts, and once weekly this procedure was supplemented by manual epilation under a Wood's filter at the clinic. Progress was satisfactory from the first, the patients experiencing less irritation and less scaling within two weeks of starting therapy. At the end of the third month, when it was thought that an irritant might stimulate the tissues to the formation of antibodies, it was decided to alternate the thymol with 4 per cent chrysarobin in chloroform, chrysarobin being an effective irritant and antiparasitic.

Therapy was continued for a year in each case, at the end of which time regrowth of hair was permitted. The thymol solution was applied twice weekly during the period of regrowth. Repeated examinations under a Wood's filter have failed to reveal any fluorescence. Microscopic examinations and cultures have failed to reveal the presence of the fungus over a period of one year in Case 1 and

a period of three months in Case 2. Regrowth of normal hair has occurred in many parts of the previously affected areas.

SUMMARY

Two cases of favus are reported that had apparently been acquired in Massachusetts.

The microscopic and cultural characteristics of the *Achorion* responsible for the disease are outlined.

A method of therapy that proved successful is described.

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MEDICAL PROGRESS

ENDOSCOPY (Concluded)*

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ESOPHAGOSCOPY

Surgery. In an editorial on Russian surgeons and Russian surgery,³⁸ it is reported that surgery is done on a vast scale in Russia. It is stated that Yudin performed in one morning three operations of replacement of esophageal stricture by jejunum. This is certainly an amazing feat.

Carcinoma. Carcinoma of the esophagus is said to be seventh in frequency in types of carcinoma among males. Operative treatment is the only method of cure. With improved technic any segment of the esophagus can now be successfully removed surgically. As pointed out in the last year's report,¹ Wookey³⁹ has discussed a technic for removing the hypopharynx and upper esophagus. Early diagnosis is the most important factor in obtaining cure. All patients with difficulty in swallowing should have early x-ray examination and esophagoscopy with biopsy to establish a positive diagnosis.

Smithers, Clarkson and Strong⁴⁰ report in detail 54 cases of carcinoma of the esophagus in which roentgenologic therapy was given. Strikingly favorable responses were noted in many cases, and most of the patients showed improvement.

Pohle and Benson⁴¹ also report on the results of radiation therapy in 85 cases of cancer of the esophagus. There were no cures. One patient, however, with cancer at the upper end of the esophagus treated by roentgenologic irradiation alone was alive and well for more than four years, and another treated by roentgenologic irradiation and implantation of radon seeds was alive and well for more than seven years. In both cases the diagnosis was confirmed histopathologically.

Benign tumor. Adams⁴² reports an interesting case of fibroma of the esophagus in a forty-one-year-old woman who complained of difficulty in swallowing of seven years' duration. After a preliminary x-ray examination and esophagoscopy, a gastrostomy was performed and a tumor measuring 5 by 7 cm. was removed by the transthoracic route. Compared with cancer, dysphagia is much slower to appear.

Pain. Moersch and Miller⁴³ point out that esophageal pain may occur in a variety of esophageal disturbances. It varies in character, intensity and distribution. It is influenced by many extraneous factors and may closely mimic the symptoms produced by other types of serious organic disease. One of the greatest obstacles in the clear understanding of the problem of esophageal pain is the knowledge concerning innervation of

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Peptic ulcer. Allison, Johnstone and Royce⁴⁴ report 10 cases of simple peptic ulcer of the lower end of the esophagus. All the patients complained of dysphagia, and in each case the cause was found to be cicatricial stenosis of the esophagus and simple ulceration, the latter being associated with chronic esophagitis and chronic gastritis. In each case the narrowing of the esophagus was associated with shortening so that a part of the stomach was pulled up into the mediastinum. The suggestion is made that this deformity, usually referred to as "congenitally short esophagus," may be acquired as the result of ulceration and scarring.

Cleaver⁴⁵ reports 10 cases of peptic ulcer of the esophagus, with pain, hematemesis and dysphagia. The pain was usually in the region of the epigastrium and at times radiated forward and around to the back. Rapid, fatal hemorrhage owing to erosion of the aorta rarely occurred; bleeding was usually much less severe. Dysphagia was mild or severe, and swallowing finally became impossible. Two complications were usually seen: perforation of the ulcer into the pleura, pericardium or bronchus and acute mediastinitis due to spread of infection from the ulcer into the surrounding tissues. The diagnosis was generally based on the symptoms and x-ray findings on swallowing barium. Esophagoscopy, although not mentioned in the summary, is considered indispensable in the differential diagnosis.

Scleroderma. Lindsay, Templeton and Rothman⁴⁶ have collected 16 cases of diffuse scleroderma, in all of which there was difficulty in swallowing. They had 5 patients of their own, only one of whom had any complaints referable to swallowing. In the other four the symptoms were clearly brought out in questioning, but the comparative severity of the pain and discomfort from the cutaneous lesions caused the difficulty in swallowing to be overlooked. In 3 of the 5 cases difficulty was experienced in introducing the esophagoscope under local anesthesia. This difficulty appeared to be due in part to inability to open the mouth more than about half the normal width or to extend the tongue beyond the mucous-membrane margin of the lower lip and tightness of the skin over the jaws and neck. In addition, none of the patients were able to produce relaxation of the cricopharyngeus sphincter by swallowing. Under general anesthesia, however, the sphincter relaxed easily and the walls in that region appeared grossly normal. Some form of general anesthesia appears to be indicated for esophagoscopy in cases of this type. In all cases, the wall of the esophagus from the beginning of the middle third downward was diffusely reddened and apparently thickened, with a lessened tendency to form normal folds. In the lower third there was a diffuse layer of white exudate, that could be easily separated off, leaving a granulating base.

In summary, these authors report that the disturbances of the esophagus are characterized by

loss of peristalsis in the lower two thirds, with relaxation and mild dilatation of the lower two thirds down to the phrenic ampulla and probably son atony of the cardiac sphincter as a direct result of the sclerodermatic process; difficulty in swallowing solids or liquids, especially when in the lying position, owing to delayed emptying of the esophagus; burning pain behind the sternum about an hour after meals, which is worse on lying down and particularly on lying on the left side, probably owing to regurgitation of gastric contents into the esophagus and resulting chronic esophagitis; chronic ulceration in the lower third of the esophagus, localized chiefly in the region just above the phrenic ampulla, and probably a direct result of the esophagitis, with sclerodermatic changes as a predisposing factor; and stricture formation in the later stage limited to the region immediately above the phrenic ampulla of the esophagus. Biopsies revealed changes in the submucosa that suggested sclerodermatic change.

Esophagitis. Paul⁴⁷ has studied the roentgenologic aspects of acute and chronic esophagitis. He believes that the acute ulcerative type is most frequently associated with peptic ulcer or develops immediately following upper-abdominal operation. Anything that tends to cause relaxation of the cardia, permitting acid gastric juice to come in contact with the esophageal mucosa, may predispose to its development. Frequent vomiting is an important factor. The use of a negative-suction apparatus in itself is of questionable value but may play a part when additional causes are present. The x-ray appearances, according to Paul, consist of severe spasm of the distal part of the esophagus; loss of mucosal folds and a fine roughening of surfaces. The lesion tends to progress to a fibrous stricture. Chronic esophagitis of sufficient severity to be the cause of symptoms is uncommon. If it is present for a sufficient length of time, the x-ray findings may be those of a diffuse fibrous stricture since the esophagus when involved by infection shows a great tendency toward the development of fibrosis. In other cases of chronic esophagitis the most striking x-ray manifestation is intermittent, diffuse spasm of the lower half or third with thickening of the mucosal folds.

Foreign body. Weaver⁴⁸ reports an interesting case in which a chicken bone remained in the esophagus for fifty-six days without perforation. This case is remarkable in view of the fact that bones are especially liable to cause esophageal perforation. The patient was a man of thirty-nine who complained of constant dull pain in the region of the epigastrium, which became worse in swallowing. The bone was removed without difficulty by esophagoscopy under local anesthesia. The postoperative course was uneventful.

Nervous disorders. Hurst⁴⁹ believes that hysterical dysphagia is rare. When it does occur, the patient

has had an incident that drew his attention to the normally automatic act of swallowing. Dysphagia may occur in various organic nervous diseases as a result of paralysis of the muscles concerned in the first and second stages of swallowing. Motor neuron disease, which includes progressive muscular atrophy and amyotrophic lateral sclerosis, may be accompanied by dysphagia if the vagal nucleus is involved in the last stages of the common form that begins in the muscles of the hands. It occurs in progressive bulbar palsy and in myasthenia gravis. Hurst believes that the most frequent nervous disorder of swallowing is achalasia, commonly known in America as cardiospasm. In the treatment of this condition he keeps mercury bougies in the esophagus for fifteen minutes just before each meal for two weeks, after which the frequency of the instrumentation is gradually decreased. The patient himself passes the bougie.

Vines and Olsen⁵⁰ report a case of cardiospasm with associated pellagra. They discuss the possible role of vitamin deficiency in cardiospasm, but in their experience favorable results were not obtained by giving vitamin B₁ to 2 patients with esophageal obstruction. When obstruction at the cardia is relieved and the patient is maintained on a normal diet, caloric deficiencies and vitamins take care of themselves.

Hiatus hernia. Vinson⁵¹ calls attention to dysphagia from hiatus hernia. In patients with the short esophageal type of diaphragmatic hernia, dysphagia results from spasm or stricture at the junction of the esophagus and the hernial sac. In those with hernia of the paraesophageal type, it results from stricture in the lower portion of the esophagus, spasm at the cardia or pressure from the herniated portion of the stomach on the lower part of the esophagus.

Extrinsic pressure as a cause of dysphagia. Tinney, Schmidt and Smith⁵² report a case of mitral stenosis in which the onset of the illness and the clinical course were dominated by difficulty in swallowing. This symptom became so severe that for nine days prior to the patient's admission to the clinic she was unable to take solid foods and was able to swallow liquids only with difficulty. On roentgenoscopic examination of the esophagus filled with barium, there was no evidence of an intrinsic lesion, but the lower third of the esophagus was displaced posteriorly and compressed by a hugely dilated left auricle. The patient received only partial relief from the dysphagia following treatment of the congestive failure.

Esophagobronchial fistula. Clerf, Cooley and O'Keefe⁵³ call attention to the four main groups of fistulas, — congenital, neoplastic, infectious and traumatic, the first two being by far the most frequent. They report 2 cases in which esophagobronchial fistula existed for nine and thirty-two months, respectively. No definite cause could be demon-

strated, although one patient had a pulmonary abscess and coughed up a mass of necrotic tissue immediately preceding the development of symptoms. There was no apparent tendency for the fistula to close after the esophagus was placed at rest. Prompt closure of the esophageal end of the fistula resulted following the esophagoscopy application of a sodium hydroxide crystal fused on a curved metal applicator and carried into the fistula for a distance of several centimeters. Both patients had subsequently been free from symptoms for more than eighteen months.

According to Haight and Towsley,⁵⁴ the surgically ideal plan for the correction of congenital atresia of the esophagus with tracheoesophageal fistula is a reconstruction of the continuity of the esophagus by an extrapleural ligation of the fistula and an end-to-end anastomosis of the esophageal segments. The first successful case of reconstruction of the esophagus by this plan is presented. The factors pertaining to operative correction of the anomaly and experiences in a series of 15 cases are discussed.

GASTROSCOPY

Normal stomach. Fitzgibbon⁵⁵ studied 40 healthy volunteers and found that 38 had mucosa within normal limits. Pigment spots and mucosal hemorrhages were not found and traumatic areas were insignificant, as contrasted with the tendency to bleed on slight trauma in gastric cases.

Technic. Moersch⁵⁶ has found that portions of the stomach that otherwise might not be adequately visualized by means of the gastroscope can often be brought into view by palpation. This method is of particular value in dealing with the antral portion of the stomach, and especially in examination of a stomach on which operation has been performed. The method is simple and causes the patient no distress. It is also of value in that it enables the examiner to determine the flexibility of the gastric mucosa. The information thus gained may be of assistance in distinguishing between a carcinomatous and an inflammatory type of infiltration.

Evaluation of gastroscopy. In a discussion on the use of the gastroscope as a supplementary aid to x-ray examination, Cohn and Levitin⁵⁷ point out that there are limitations to the x-ray diagnosis of gastric lesions that are not usually appreciated. Gastroscopy is of great assistance in clarifying certain doubtful roentgenologic findings and in differentiating others. It brings into direct vision lesions that cannot be demonstrated by x-ray. Benign ulcers have a gastroscopic appearance different from that of malignant ulcers. Carcinoma can be diagnosed and classified and the extent of involvement determined before surgery, information thus being obtained regarding its operability and prognosis. The course of a benign ulcer as regards its healing Polyps

rarely diagnosed by x-ray can be visualized by gastroscopy and their extent determined. Malignant tumors of the stomach can be differentiated from intragastric and extragastric lesions. The hypertrophic and atrophic types of gastritis can be diagnosed only by gastroscopy. Following operation, lesions such as marginal ulcers and gastritis are ordinarily diagnosed only with difficulty. The gastroscopist can diagnose both these conditions and differentiate the distorted folds of the postoperative stomach from an ulcer. The authors conclude that gastroscopy is a simple, safe procedure and is a valuable supplement to x-ray examination.

Balfour,⁵⁸ in discussing the annual report of the Mayo Clinic on surgery of the stomach and duodenum, states that gastroscopy has not only been a distinct aid in early diagnosis of cancer but has also furnished valuable information on the significance of gastritis in relation to the development of carcinoma. One may expect that the continued use of this procedure will result in a better knowledge of the factors that predispose to cancer of the stomach.

Howard⁵⁹ discusses gastroscopy and the use of the gastroscope in the military services, stating that in the diagnosis and treatment of gastric ulcers the gastroscope is of course helpful. He also states that American physicians agree that gastritis is best diagnosed by inspection of the mucosa through the gastroscope. Tumors and ulcerations, some of which escape detection by roentgen rays, are readily visualized. The easy detection of gross gastric lesions establishes the gastroscope in its merited place in the military services and does much to promote its use in civil work.

Paulson⁶⁰ reaches similar conclusions regarding the present position of gastroscopic diseases, concluding that gastroscopy is complementary to roentgen-ray examination for diagnosis. When the roentgenograms are negative and yet suspicion of abnormality persists, gastroscopy may reveal an occasional neoplasm, erosions, peptic ulceration or gastritis. These lesions may also account for otherwise unexplained hemorrhage and a duodenal-ulcer syndrome not due to duodenal ulcer. When roentgenograms are positive, gastroscopy makes possible confirmation; a nicer differentiation grossly between benign and malignant lesions; a clearer delineation of the site and extent of the lesion, which helps to determine the question of operability; the differentiation grossly of spasm and edema from the lesion itself; and the occasional detection of an associated gastritis that may account for atypical symptoms, often erroneously ascribed to a defect of the roentgenogram in the duodenal cap but due to a healed, scarred ulceration.

Gill⁶¹ in an analysis of 1000 gastroscopic examinations concludes as follows:

In gastric ulcer, the gastroscope may reveal ulcers not otherwise demonstrable, and affords proof of healing more cheaply and accurately than any other method.

In chronic gastritis, gastroscopy provides confirmation not otherwise obtainable and enables differentiation of and degree of severity, essential for satisfactory disposal of treatment. Mucosal atrophy can only be diagnosed any degree of certainty by gastroscopy.

Multiple gastric erosions are only rarely demonstrated by x-rays, but by gastroscopy lesions of some significance can be diagnosed and differentiated into the chronic acute, and disposal can be made accordingly.

In other Service cases, less numerous but no less important, gastroscopy may offer the only means of diagnosis. These include early gastric carcinoma, benign gastric tumors, postoperative dyspepsia, unexplained gastric hemorrhage and achlorhydria.

Pollard and Lopes Pontes⁶² have reached somewhat similar conclusions — namely, that gastroscopy and roentgenology, as the only direct diagnostic procedures for the detection of gastric ulcer, should be concurrently employed. Although x-ray examination reveals the lesion a little more frequently, gastroscopy appears to make it possible to discriminate between a benign and a malignant lesion in a higher proportion of cases. Both methods have their own limitations and so-called “blind spots.” Gastroscopy is the only reliable method available for the diagnosis of a primary or associated gastritis. It is also of considerable help in the recognition of certain types of localized gastritis. Roentgenologically may simulate a neoplastic formation.

Gastritis. Gray⁶³ studied the epigastric symptoms in alcoholic patients with and without gastric ulcer and found that only 7 per cent of the group of normal stomachs had symptoms referable to gastrointestinal tract, whereas 53 per cent of patients with chronic gastritis and 60 per cent of those with severe gastritis had gastric complaints. It therefore appears from these studies that there may be a direct relation between gastritis and incidence of symptoms in chronic alcoholic addiction.

In last year's report,¹ Benedict's⁶⁴ article on hypertrophic gastritis was reviewed. In a discussion of this paper Carey⁶⁵ stated that the picture described agreed with his own experience in that the symptoms are similar to those of ulcer. Night pain, radiation of pain were seen less frequently by Carey than by Benedict.

Spriggs and Marxer,⁶⁶ in a monograph on polyps of the stomach and polypoid gastritis, state their belief that polyps are prone to malignant degeneration. Such a change was reported in between five and one in six of the series. The diagnosis of a polyp or polyps is made by radiology and suitable cases, by gastroscopy. Polypoid gastritis usually responds to treatment, which includes dietary measures, elimination of alcohol and in some cases gastric lavage.

Kantor⁶⁷ believes that positive gastroscopic evidence of gastritis in a front-line soldier should entitle him “to every consideration and to every benefit.”

Gold⁶⁸ made a gastric study in 50 soldiers with dyspepsia and reported that gastroscopy is the only reliable method available for the study

stritis. Hemorrhage from gastritis is not a rare occurrence. Further studies, he says, are indicated regarding the incidence of gastritis in military forces, the effects of therapy and the interference of symptoms with the performance of duty.

Although it has been possible to correlate fairly accurately the gastric findings in gastritis with the post-mortem findings (Benedict and Mallory⁶⁹), it may not be so easy to account for the symptoms on a pathological basis. In this connection Ortmayer⁷⁰ pointed out that it would be difficult to correlate such symptoms with relatively minor pathologic changes, such as nonulcerating gastritis, probably because the pain threshold of the stomach is high. Even a striking lesion, such as a deep gastric ulcer, may not produce symptoms. Ulcers may be painful on one day and not at all painful on the next. It is timely to emphasize in this regard, as Renshaw⁷¹ and Wilkinson⁷² have done, that patients as a whole, not "stomachs," are being treated.

Relation of chronic gastritis to cancer of stomach. A number of observers have stated that carcinoma of the stomach does not develop on a previously healthy mucosa. Many recent reports indicate that gastric atrophy predisposes to gastric carcinoma. Among these may be mentioned that of Shapiro, Schiff, Maher and Zininger,⁷³ who found microscopic evidence of atrophic gastritis in 28 (80 per cent) of 35 cases of gastric cancer. They believe that the frequent coexistence of atrophic gastritis and gastric cancer strongly suggests a relation between them, the nature of which has yet to be determined.

Westhues,⁷⁴ on the basis of 463 resected stomachs and 40 stomachs obtained by autopsy, concludes that inflammation is not the decisive factor in the development of gastric cancer. The blastomatous gastric polyps, which are definitely precancerous in nature, are likewise not inflammatory, and cancers developing from them are not the result of inflammation. Westhues does not deny the possibility of development of cancer on the basis of gastritis.

Doehring and Eusterman⁷⁵ record the results of their observations on 40 patients with associated pernicious anemia and carcinoma of the stomach, studied at the Mayo Clinic. Of 1014 patients with pernicious anemia, 17 had carcinoma of the stomach, an incidence of 1.7 per cent, or slightly higher than that of gastric carcinoma in the general population. Carcinoma associated with pernicious anemia was found to be of a similar grade of malignancy and in the same location as carcinoma uncomplicated by pernicious anemia. Pernicious anemia usually sets in at about the age of fifty-four, while signs of cancer appear at the average age of sixty-three. Gastric carcinoma in association with pernicious anemia is becoming more frequent, probably owing to the fact that modern methods of treatment prolong the period of survival long enough for

carcinoma to set in. Achlorhydria is invariably found with pernicious anemia and usually with gastric carcinoma. The cancer usually develops in the pyloric region. It develops with less frequency in the middle third of the stomach, and is most rarely discovered in the upper third. All the cases studied were adenocarcinoma. Benign tumors or polyps develop fairly often in cases of pernicious anemia.

White⁷⁶ reports a case of pernicious anemia of long standing in which both carcinoma and tuberculosis of the stomach were found at operation. This is the tenth verified case of gastric tuberculosis encountered at the clinic and the second verified case of carcinoma and tuberculosis in the same stomach. In commenting on this case, Walters⁷⁷ remarks that in pernicious anemia it is the associated gastritis that is of concern. Gastroscopists have offered additional proof of the possible precancerous nature of gastritis. Schindler⁷⁸ has found gastric adenomas in 6 per cent of the cases of atrophic gastritis, whereas these adenomas occurred in less than 1 per cent of cases in which atrophic gastritis was not present. In addition, adenomas of the mucosa occurred in 14 per cent of cases of pernicious anemia.

Brindley, Dockerty and Gray⁷⁹ report a case of multiple carcinoma of the stomach in which examination of the resected specimen revealed four adenocarcinomas of different degrees of malignancy. In this case diffuse advanced chronic gastritis may have been a precursor of the multiple carcinomatous lesions. Credence is given to this supposition by the diffuse nature of the chronic gastritis, particularly with reference to the pronounced hyperplasia of mucous cells, and by the presence of multiple lesions of all four grades of malignancy.

Freedman, Glenn and Laipply⁸⁰ report 5 cases of atrophic gastritis simulating gastric carcinoma. They emphasize that the localized form of hyper-trophic gastritis may be difficult to differentiate from carcinoma. Even gastroscopically, this differentiation cannot always be made. The diagnostic difficulties were such that carcinoma could not be excluded before an exploratory laparotomy was done. In 3 of the cases, the true nature of the lesion did not become apparent until histologic examination of the resected specimens was made. Chronic gastritis is in some cases a curable precancerous condition. Patients should be carefully followed with repeated x-ray and gastroscopic examinations.

Gastric ulcer. In a discussion of the treatment of gastric ulcer, Judd and Priestley⁸¹ point out that in certain cases all the main differential points between benign and malignant gastric ulcerations, including x-ray examination and gastroscopy, may be misleading. They believe that medical treatment of presumed gastric ulcer leaves much to be desired. The error in the preoperative diagnosis of gastric ulcer in differentiation from

cer is approximately 10 per cent. Only approximately half the cases treated medically for gastric ulcer show results that these writers consider entirely satisfactory, and about 10 per cent of them subsequently prove to have carcinoma. The results of the surgical treatment of gastric ulcer are entirely satisfactory in the majority of cases. Since the operative mortality of gastric resection in Judd and Priestley's experience has been only 2.5 per cent, they are increasingly in favor of surgical treatment.

Duodenal ulcer. Tumen and Lieberthal⁸² made gastroscopic studies of 50 patients with duodenal ulcer uncomplicated by pyloric obstruction. Of these, 33 had chronic gastritis, 1 had unclassifiable inflammatory changes and 16 had normal stomachs. The presence of gastritis did not regularly influence the clinical course of duodenal ulcer. It was impossible to postulate the presence or absence of associated gastritis on the basis of the nature of the symptoms or the character of the response to treatment.

Carcinoma. Schiff⁸³ believes that the diagnosis of gastric diseases has been greatly aided by the use of the gastroscope. In carcinoma it is helpful not only in detecting the presence of the tumor but also in determining its location, character and extent. The gastroscope is also of value in excluding the presence of cancer in suspected cases, thus frequently preventing unnecessary operation. The best results are obtained by co-ordinating the findings of gastroscopic and roentgenologic examinations.

Pack and McNeer⁸⁴ in a discussion of total gastrectomy for cancer point out the value of the esophagoscope and the gastroscope in determining the region of the growth either in the esophagus or in the stomach. If the x-ray studies show the upper third or more of the stomach to be pliable and apparently uninvolved, the flexible gastroscope may be safely introduced. It is often helpful in forming an idea concerning the amount of uninvolved stomach superior to the cancer. If the lesion extends high or if the esophagus is involved, the flexible gastroscope should not be used, because it is introduced blindly and so may traumatize the cancer and cause hemorrhage or perforation. The rigid esophagoscope of the Janeway or Jackson type is safer to employ under these circumstances, since it is passed down the esophagus under direct visual guidance at all times. Furthermore, it is possible to obtain a biopsy through this instrument. By measurement from the upper incisor teeth, one can determine the exact location of the superior margin of the cancer.

For several years partial gastrectomy by the transthoracic approach has been recognized as an outstanding contribution to gastric surgery. Sweet⁸⁵ has recently reported 7 cases of total gastrectomy by the transthoracic route. Diagnostic esoph-

gосcopy and gastroscopy in addition to x-ray examination may be extremely helpful in establishing the diagnosis and planning the surgical approach and in determining operability. Peritoneoscopy is also important as a means of excluding liver metastases before major surgery.

Experimental studies. Paul⁸⁶ studied 107 patients with normal gastric mucosa by gastroscopy and found that acetylsalicylic acid caused no hyperemia, edema or hemorrhage even in daily doses as high as 80 gr. The ingestion of the drug over long periods of time does not produce chronic gastritis, and the epigastric distress that sometimes occurs after the ingestion of acetylsalicylic acid may be the result of increased acid production and pylorospasm.

Layne and Carey⁸⁷ made an endoscopic study of the appearance of the gastric mucosa in the anesthetized dog, concluding as follows:

The presence of foreign material or food in the stomach causes an appearance of hyperemia with congestion and excess secretion of mucus.

Inflation flattens the mucosal folds and often brings blood vessels into view.

A diet of coarse food, such as hospital scraps, produces hyperemic, granular changes in the gastric mucosa. The gastric mucosa appears normal only when the dog is fed dog biscuits.

Atropine decreases the quantity and changes the character of gastric secretion and diminishes gastric tone.

Pilocarpine augments the amount of gastric secretion and increases gastric tone.

Benzedrine produces transient hyperemia of the gastric mucosa and decreases gastric tone slightly.

Alcohol induces generalized hyperemia of the gastric mucosa, which subsides after about five weeks. The gastric mucosa thereafter remains normal even with continued administration of alcohol.

Although it is manifestly impossible to review adequately the volume by Wolf and Wolff⁸⁸ entitled *Human Gastric Function*, this report would not be complete without mentioning the importance of their contribution. This book is based on a study of a patient with an esophageal stricture who had fed himself through a gastric fistula for forty-seven years. It is a modern continuation of the work of Beaumont, Richer and Carlson, with special reference to the significance of the psychosomatic influences on gastric functions. The character of the subject's defect offered an excellent opportunity for a prolonged close inspection of the stomach mucosa by virtue of the large size of the defect and also because of the collar of mucous membrane that lay exposed on the abdominal wall. Changes in vascularity were readily recognized by variations in the color of the mucous membrane. Accelerated blood flow in the mucosa was not merely associated with blushing of its surface; the membrane itself became wet, swollen, and turgid, and the rugae were slightly fuller and smoother. These evidences of vascular engorgement were especially obvious in the collar of mucosa exposed on the abdominal wall. During marked hyperemia, it often doubled in thickness (from 5 to 10 mm.) and its radial folds

decreased in number from twelve or thirteen to five to seven. The tissue itself under such circumstances felt succulent and boggy.

The correlation of motor activity and blood flow was demonstrated under different conditions, such as distention of the stomach, mechanical irritation, ingestion of food and swallowing. Hyperfunction of the stomach, either motor or secretory, was always accompanied by hyperemia.

Varying emotional states may be associated with profound alterations in gastric functions. In the evaluation of the effects of drugs, the prevailing affective state of the patient at the time, the circumstances surrounding the experiment and the patient's reaction to the mode and implication of the administration of the drug, as well as his reaction to its side effects, were found to be of first importance.

Changes in gastric function in reaction to various situations and accompanying emotional states are presented in detail. Observations on the collar of the mucosa were made during a discussion of appetizing foods, alarm reaction (fear), depressive thoughts, resentment, hostility, anxiety and so forth. The alterations in gastric function fell into two categories: depression of acid output, motor activity and vascularity; and acceleration of these functions. The former was associated with a reaction of flight or withdrawal from an emotionally charged situation. The latter accompanied a reaction of internal conflict, with an unfulfilled desire for aggression and fighting back. Profound and prolonged emotional disturbances of this kind were accompanied by marked and prolonged increases in gastric motility, secretion and vascularity, with reddening and engorgement of the mucous membrane, often reproducing the picture of gastritis. This picture was induced by vasomotor changes resulting in hyperemia and congestion of the mucosa. The protective power of mucus was demonstrated. An appearance simulating chronic peptic ulcer was produced by exposing a peripheral edge of the collar of mucosa continuously to the digestive action of gastric juice for four days. After the ulcer and the surrounding area had been covered with a protective petrolatum dressing, complete healing took place within three days, leaving no trace of the lesion.

The following conclusions were rendered from this study:

Undue and prolonged acceleration of acid secretion in the stomach, however provoked, resulted in hyperemia and engorgement of the mucous membrane resembling hypertrophic gastritis. The mucosa in this state was unusually susceptible to injury, and even the most trifling traumas resulted in hemorrhages and small erosions. Ordinarily the mucosa was protected from injury by an effective coating of mucus; loss of this protection in the face of minor traumas led to edema, inflammatory changes, erosions and hemorrhages. Contact of acid gastric juice with a denuded surface induced further hyperemia and acceleration of acid secretion. Prolonged

contact of acid gastric juice with a minor erosion resulted in the formation of a peptic ulcer.

PERITONEOSCOPY

Technic. Harken and Glidden⁸⁹ used transparent collapsible plastic balloons in various sizes and shapes on the cardioscope. These balloons may be applicable for peritoneoscopy, as suggested by Lamb⁹⁰ in 1941.

Cirrhosis. One of the most valuable uses of the peritoneoscope is in the study of cirrhosis of the liver and the differential diagnosis from carcinoma. In this connection it is interesting to note the frequency of cirrhosis of the liver as reported by Peller.⁹¹ This author found among the records of 6596 cases in the Bellevue Hospital, New York City, covering the period from 1934 to 1941, cirrhosis of the liver in 9 per cent of the patients over twenty years of age. Malignant tumors were found in 17 per cent of these patients.

Amberg⁹² discusses the prognosis of chronic hepatitis in children, stating that early acute hepatitis usually heals. It may progress and develop into diffuse necrosis of the liver, of which acute, subacute, subchronic and chronic forms have been distinguished. The chronic form has been interpreted as healing of the necrosis with development of cirrhosis of the liver. Cirrhosis has been defined as a progressive lesion that involves parenchymatous degeneration and fibrous and parenchymatous repair and sooner or later causes death. Unfortunately, most of the cases of chronic hepatitis that Amberg encountered were of this kind. In summary, the author reports that chronic hepatitis of children ending in cirrhosis fairly frequently extends over a period exceeding five years. It seems possible that the disease need not always end in cirrhosis but may heal. In my opinion, information regarding hepatitis and cirrhosis in children as well as in adults will be obtained by the increasing use of peritoneoscopy together with biopsy of the liver.

Kirshbaum and Shure⁹³ have reported 356 autopsy cases of alcoholic cirrhosis. The ratio of males to females was 2:1. In 42 per cent of the cases, a history of chronic alcoholism was obtained. Jaundice was present in 48 per cent, and ascites in 59 per cent. Hypertrophic livers were noted in 62 per cent, and atrophic livers in 38 per cent. All the spleens were enlarged. In 11 cases, primary carcinoma of the liver was encountered as an incidental finding.

Ascites. Meigs, Armstrong and Hamilton⁹⁴ have listed 27 cases of fibroma of the ovary with fluid in the abdomen and chest — Meigs's syndrome. The syndrome is of considerable importance, because some patients have failed to obtain proper surgical relief, whereas others, originally doomed because of a tumor considered inoperable, are now well. Undoubtedly peritoneoscopy would be of value in the diagnosis of some of these cases, especially in the differentiation of this condition and carcinoma.

nomatosis, tuberculous peritonitis, cirrhosis of the liver and other diseases in which ascites may be present.

Jaundice. White⁹⁵ has made a study of errors in the diagnosis of jaundice, limiting his paper to 175 cases that came to operation or autopsy. Peritoneoscopy was used in only a small number of cases. Over half the errors were associated with a diagnosis of cancer. Too many diagnoses of cirrhosis were made when latent cancer was present. Errors in diagnosis were made in 14 cases (8 per cent). Judging from the kind of errors reported, it is evident that a more frequent use of the peritoneoscope would have eliminated many of them.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

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CASE 30221

PRESENTATION OF CASE

A fifty-three-year-old housewife entered the hospital because of right-sided paralysis.

The patient was known to have had hypertension. Six or eight months before entry she was seen in the Eye and Ear Infirmary for cataract and possible separation of the left retina. The day before admission she suddenly found herself unable to speak. She then developed paralysis of the right side of the body. No other information was available.

Physical examination showed a well-developed, obese woman who was unable to speak but who appeared conscious of her surroundings. A mature cataract of the left eye was present. There was flaccid paralysis of the right leg. The right arm and hand moved only slightly. There was no facial asymmetry. The biceps, triceps, radial and ankle tendon reflexes were decreased on the right. The right patellar reflex was absent. The plantar reflexes were decreased on the right and increased on the left. There was no Kernig sign. A questionable right temporal hemianopsia was present. She could not swallow. Ophthalmologic examination showed the right fundus to have an old hemorrhage at ten o'clock. The vessels were tortuous. There was arteriovenous nicking. The left fundus could not be visualized. The heart was rapid. No other findings were recorded.

The blood pressure was 200 systolic, 125 diastolic. The temperature was 100°F., the pulse 120, and the respirations 25.

Examination of the blood showed a white-cell count of 21,400. The urine was acid, with a specific gravity of 1.024 and a + test for albumin. The sediment was negative. A blood Hinton test was negative. The nonprotein nitrogen was 27.5 mg. per 100 cc.

The patient was given 500 cc. of 5 per cent dextrose in saline intravenously the first day, and between 700 cc. and 1500 cc. of the fluid daily thereafter. She was fed by an indwelling Levine tube. On the sixth hospital day she developed diarrhea, which may have been due to an intake of 200 cc. of fluid by mouth at one time. Her condition other-

*On leave of absence.

wise remained essentially the same until the ninth hospital day, when the temperature rose to 103°F., the pulse to 136, and the respirations to 40; the blood pressure fell to 110 systolic, 88 diastolic. Examination at that time showed rapid, grunting respirations. The face was flushed. The lips and nails were cyanotic. There was herpes on the lips, and some jaundice. Many coarse, snapping rales were heard at the left base posteriorly and over the axilla, without dullness. The point of maximal cardiac impulse was felt 11 cm. to the left of the midline. The rate was rapid. The aortic second sound was equal to the pulmonic. No murmurs could be heard. The abdomen was negative. The right leg was edematous, with tenderness in the calf and a positive Homans's sign. The right superficial femoral veins were hard and tender medially above the knee.

A portable x-ray film of the chest showed questionable dullness over the left midlung field, but this could not be definitely determined. Femoral-vein ligation was deemed inadvisable. The patient was given 5 gm. of sulfadiazine intravenously on the ninth and tenth days and 2.5 gm. on the eleventh day. On the twelfth day the urinary output fell to 500 cc. on an intake of 1500 cc. The blood sulfadiazine level on the twelfth day was 40 mg. per 100 cc. The temperature came down to normal, but the urinary output remained low. Intravenous fluids, sodium lactate and high intravenous vitamins failed to affect urinary excretion. The sulfadiazine level was 9 mg. per 100 cc. on the fifteenth hospital day. On the seventeenth hospital day she became stuporous. The nonprotein nitrogen was 89 mg. per 100 cc., and the protein 6.7 gm. She became comatose and died on the eighteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. ARTHUR WATKINS: In this case we are called on to explain a sudden right hemiplegia followed by death eighteen days later. The only information in the past history reveals a hypertension of unknown duration and a cataract of some eight months. The latter I cannot connect with the final illness. The hypertension, however, I should expect to have been directly responsible for the symptoms—the loss of speech followed by right hemiplegia within a day and unassociated with loss of consciousness. The speech loss alone might have been due to a relatively discrete lesion in the motor speech area of the cortex in the left frontal lobe in a right-handed patient. This could have been embolic or due to a small hemorrhage or thrombosis. A rather complete right hemiplegia developed within twenty-four hours, and if also due to a cortical lesion it would have involved an area sufficiently large, one would presume, to have caused loss of consciousness. It seems more likely that the hemiplegia was due to hemorrhage in the internal capsule.

I am not given sufficient data to distinguish between cortical or subcortical types of aphasia, or for speech loss due to a bulbar lesion. To connect it with the hemiplegia, the lesion could have been subcortical. There was a complete flaccid type of paralysis of the lower extremities — often seen in the early stages of hemiplegia — and nearly complete paralysis of the upper extremity. The fact that the leg was more involved than the arm also points to a subcortical lesion, as the cortical areas for speech and leg movement are quite separated.

In view of the acute onset and the known vascular disease, I can see no reason to consider brain tumor. There was no facial asymmetry, presumably, at rest. I would like to know if the movements were normal. It seems unlikely to me that they were. We are told nothing of the other cranial-nerve functions. The tendon reflexes were diminished or absent, which is in keeping with the flaccid type of paralysis. The description of the plantar reflexes is ambiguous. Without knowing whether the movement of the great toe was an inflection or an extension, I can only guess that there was a slight plantar reflex or Babinski on the right, and a quite definite one on the left. Both reflexes were therefore pathologic. If this assumption is correct, it is of great importance in localization.

The patient was unable to swallow although conscious, which is an unusual finding in hemiplegia. One immediately suspects a bulbar palsy from involvement of the nucleus of the lower cranial nerves. In such a case the lesion would have to be below the level of the seventh nerve. With complete paralysis one would expect a contralateral sensory loss. We do not know anything about the sensory findings and they would have been hard to test in this patient.

A most significant finding was the right temporal hemianopsia. This immediately locates the lesion above the brain stem, probably in the optic radiations. Hemianopsia in this area, however, would not cause loss of swallowing because of the bicortical representation of the cranial nerves. I therefore conclude that there was bilateral involvement of the cortical tracts, giving a pseudobulbar palsy, which conforms with the bilateral Babinski tests.

There was a well-marked hypertension, and vascular changes in the eye grounds, but not much evidence of renal failure as judged by subsequent urine examination, with good concentration, a + test for albumin and a negative sediment and by a normal nonprotein nitrogen. On admission, one would presume that the likeliest diagnosis was hypertension with a cerebral vascular accident — chiefly either hemorrhage or thrombosis of the left internal capsule but with some damage to the right side of the brain. There was no evidence of valvular heart disease, and there was no apparent source of emboli elsewhere in the body.

On the ninth hospital day there was a sudden change, which is about the time that we begin to

look for pulmonary complications in patients with hemiplegia who are not getting well. In this case the pulmonary embarrassment was quite severe and there was circulatory collapse as well, with a fall in blood pressure and a rapid pulse. There were rales in the left base, and dullness. The heart was not enlarged to palpation. No mention is made of pain, cough or bloody sputum, but I still suspect pulmonary infarct. Examination of the extremities then revealed an edematous right leg, with a tender calf, and a positive Homans's sign, — pain in the popliteal space on dorsiflexion of the foot, — which at once suggests phlebothrombosis. The superficial femoral veins were hard and tender. She had fever, however, and it might have been a thrombophlebitis. I suspect the pulmonary signs were due to an embolus. The portable chest plates apparently were inconclusive.

The thrombophlebitis developed in the paralyzed leg during the first week in bed. Because of the fever I presume that it was thought that the patient had an infected pulmonary embolus or a bronchopneumonia, and sulfadiazine was given. On the third day there was diminished urinary output and an extremely high blood diazine level. In spite of intravenous fluids, the urinary excretion did not increase, the patient became comatose, and the nonprotein nitrogen rose to 89 mg. per 100 cc., and nine days following the administration of the sulfadiazine the patient died. We do not know whether there was crystalluria or hematuria. She had one negative urine examination on admission, and it is possible that the renal failure was due to sulfadiazine that had precipitated and had caused renal obstruction. There is no history of pain or swelling in the kidney region. Perhaps it is unusual to have signs of renal complication develop after only three days of sulfadiazine. I have recently, however, seen reports of cases in which intravenous diazine was given routinely to surgical patients in exactly the same dosage, 43 per cent of whom developed renal complications when alkaline therapy was not given. So it seems possible that there was a renal complication due to the precipitation of sulfadiazine crystals, with obstruction. There may have also been a toxic nephritis. We do not know whether she had had sulfa drugs previously; perhaps this would have been more likely if she had had some. Another possibility is thrombosis of the renal vessels. The patient probably did have a certain amount of acidosis; she was dehydrated and had diarrhea, which makes renal complications likelier under sulfadiazine treatment.

I therefore conclude that the patient had a cerebral vascular accident which chiefly consisted of hemorrhage or thrombosis — I cannot be sure which — into the left internal capsule; there was possibly some similar involvement on the right, resulting in a pseudobulbar palsy. She had hyper-

nion, arteriosclerosis, thrombophlebitis of the right femoral vein, with pulmonary infarction, and renal obstruction due to sulfadiazine, possibly with toxic nephritis and some thrombosis of the renal vessels.

DR. AUGUSTUS ROSE: Have you any preference between thrombosis and hemorrhage?

DR. WATKINS: Without loss of consciousness, one would probably say that thrombosis was likelier to be the cause, particularly after such an extensive hemiplegia. But a slow type of hemorrhage might do the same thing.

DR. WYMAN RICHARDSON: I think that Dr. Watkins should protect himself against the machinations of the Pathology Department by mentioning the fact that we had one patient who had a paraxial embolus to the brain through a patent foramen ovale. I am not suggesting that as the cause here, but it should be mentioned.

DR. ROSE: Occasionally, cerebral emboli occur about a patent foramen ovale and with relatively little in the way of pulmonary involvement.

DR. BENJAMIN CASTLEMAN: Emboli from pulmonary veins?

DR. ROSE: Yes. The leg vein is responsible for a pulmonary embolus, and another embolus is released from a thrombosed pulmonary vein in the affected area.

DR. CASTLEMAN: I do not remember any such cases, although it would be hard to prove.

DR. ROSE: You read about them in the textbooks.

DR. CASTLEMAN: We had a case of cerebral embolus some time ago in which we wondered about the possibility that the embolus had arisen from a pulmonary vein close to a pneumonic area.

CLINICAL DIAGNOSES

Hypertensive heart disease.

Uremia.

Thrombophlebitis.

Right hemiplegia, with aphasia.

DR. WATKINS'S DIAGNOSES

Cerebral thrombosis or hemorrhage: large lesion in left internal capsule, small one in right internal capsule.

Hypertensive heart disease.

Thrombophlebitis of right femoral vein.

Pulmonary infarction.

Renal obstruction due to sulfadiazine crystals.

ANATOMICAL DIAGNOSES

Cerebral hemorrhage.

Pulmonary embolism, acute, massive

Bronchopneumonia.

Pulmonary congestion and edema.

Pulmonary infarct, minute.

Central congestion and necrosis of liver.

Thrombosis of right posterior tibial and popliteal veins.

Cardiac hypertrophy, hypertensive type.

Jaundice

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN. The autopsy on this patient showed a thrombus in the right posterior tibial and popliteal veins. It had in part broken off and produced a massive pulmonary embolus of the left pulmonary artery, which was probably the immediate cause of death. There were a few smaller emboli in the lungs, but only one small infarct, which measured about 2 by 1 cm. There were, however, scattered foci of bronchopneumonia and edema and congestion of the lungs. The kidneys showed a moderate degree of vascular nephritis but no evidence, so far as we could make out, of sulfonamide changes.

Dr. Kubik will describe the cerebral findings.

DR. CHARLES S. KUBIK. There was a hemorrhage, measuring 5 cm. in diameter, in the left frontal lobe. It was farther forward than usual, destroying the head of the caudate nucleus, and displacing the internal capsule and lenticular nucleus backward. It had not ruptured into the lateral ventricle or subarachnoid space. A large part of the clot was brick red and rather firm, obviously representing old hemorrhage; another part consisted of the usual soft, gelatinous, dark-purplish clot of recent hemorrhage. Thus there were at least two episodes of bleeding. There were several small old infarcts; up to 3 or 4 mm. in diameter, in each lenticular nucleus. Such lesions are a frequent finding in longstanding hypertension, and do not, as a rule, cause obvious symptoms or abnormal neurologic signs. I do not know how to explain the left-sided extensor plantar response. There was no associated hemorrhage of the midbrain or pons.

I might add that this patient survived an unusually long time. In most cases of massive cerebral hemorrhage* death occurs in from a few hours to two or three days, though occasionally not until a week or ten days. Recovery almost never takes place. I believe that only two old cerebral hemorrhages have been found at autopsy at this hospital in the past fifteen years. Patients who survive a severe "shock" and are left with a residual hemiplegia or hemiparesis may, with rare exceptions, be assumed to have had a cerebral infarct.

DR. WATKINS: When do you think the pulmonary embolism occurred?

DR. CASTLEMAN: The massive one probably occurred within twenty-four hours of death. The patient may well have had one on the ninth day, associated with the fall in blood pressure and cyanosis

*A distinction is made between cerebral hemorrhage, originating within the substance of the brain, and subarachnoid hemorrhage. In the latter condition, which usually results from a leaking aneurysm, the death rate is comparatively low, probably between 25 and 30 per cent, at the time of the first attack.

It is interesting to speculate concerning the cause of the jaundice. Ordinarily when a patient with cardiac disease develops jaundice, the first thing to be considered is infarction of the lung. The jaundice is believed to be due to the inability of a congested liver to excrete the excess bilirubin produced by the hemolysis of the red cells in the infarct. Although this patient had emboli to the lung, there was only one small infarct. It is conceivable, I suppose, that the absorption of bilirubin from the cerebral hemorrhage, which had existed for eighteen days, might have been a factor in the production of the jaundice. The liver was only moderately congested; there was some central necrosis with fatty vacuolization, but not any more than one sees in many patients without jaundice.

DR. RICHARDSON: I do not believe that absorption from the cerebral lesion was enough to have caused jaundice.

DR. CASTLEMAN: Ordinarily, I should not have thought so, but it was a large hemorrhage of eighteen days' duration.

CASE 30222

PRESENTATION OF CASE

A sixty-two-year-old housewife entered the hospital because of intermittent, severe pain in the lower part of the back of seven days' duration.

The patient was in good health until about two years before entry, when she suddenly developed severe, boring pain across the upper abdomen, with nausea and vomiting of recently ingested food. The pain gradually subsided. She was asymptomatic for two weeks, and then had a recurrence of the pain, as well as the nausea and vomiting, lasting from twelve to twenty-four hours. Similar attacks recurred every three to six weeks until three months before admission, when they entirely ceased. She had no hematemesis or tarry or bloody stools. She was markedly constipated, requiring regular catharsis. A gastrointestinal series one year and three months before entry was said to have been negative.

Four weeks prior to admission she developed slight frequency and nocturia (two to four times), with a drawing, mild, nonradiating pain just above the symphysis on urination. These symptoms persisted. There was no hematuria or pyuria. At the same time she noticed brownish irregular spots in the left upper visual field. Seven days before admission she developed an intermittent, severe, burning pain in the right costovertebral angle and low back, which persisted.

She had lost 30 pounds in two years, "most of it in the past five months." She had had considerable weakness and fatigue in the two-year period, as well as occasional cramps in the muscles of the extremities. About a year and a half before admission, in a community hospital, she had a right radical mastectomy for carcinoma of the breast. Since

then her physician had treated her with iron liver for "anemia."

Physical examination showed a somewhat undernourished woman. The right radical mastectomy scar was well healed, and there was no evidence of recurrent carcinoma in the scar or in the axilla. Some lymphedema of the right arm was present. The lungs were clear. There was a hard, lobulated mass occupying the entire lower abdomen, more pronounced on the right side and extending 5 to 7 cm. above the symphysis. It was firm, hard and lobulated, and seemed fixed to the peritoneum. Pelvic examination showed a small cervix. The uterus was normal in size and anteriorly displaced. Behind it and to the right was the described mass, which measured 8 cm. in diameter and was adherent to the vagina and partially in the pelvis.

The blood pressure was 140 systolic, 75 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 2,770,000, with 8.2 gm. of hemoglobin. The white-cell count was 10,000, with 84 per cent neutrophils. The urine was negative. The sedimentation rate was normal. The stools gave a + + + + guaiac test. A blood Hinton test was negative.

X-ray examination of the chest, spine and bladder, as well as the plain films of the abdomen, was negative. An intravenous pyelogram showed prompt excretion of the dye by both kidneys, lining a nondilated pelvis, calyces and ureters on the left. The right renal pelvis and calyces were moderately dilated, and the terminal calyx was blunted. The upper half of the right ureter was visualized and showed slight dilatation. The remainder was not definitely visible below the level of the fifth lumbar vertebra, except for a small filling defect just about the ureterovesical junction. A cystogram showed a pressure defect on the right side of the bladder, apparently due to a soft-tissue mass occupying the right side of the pelvis. A cystoscopy showed a pale bladder mucosa. In the right base the ureter was apparently pushed in by an extrinsic mass, forming a projection 4 by 5 cm. The right ureter looked normal and was easily catheterized for 15 cm., when considerable urging was required. Finally passed about half way to the kidney, the catheter drained clear urine. A retrograde pyelogram showed the right ureter to be tortuous, with a sharp angle opposite the fourth lumbar vertebra. The ureter appeared narrow just below the sigmoid iliac region. No calculi were visible.

The patient was given several transfusions, and on the eighth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD HAMLIN, JR.: May we see the x-ray films?

DR. MILFORD SCHULZ: These films show slight rotation of the pelvis, calyces and upper ureter on right side. Here is the shadow of the mass occupying the right side of the pelvis, which may be responsible for the delayed emptying and abnormal filling of the kidney and ureter. There is nothing remarkable in the films of the chest except evidence of the old mastectomy.

DR. HAMLIN: We are asked to determine the nature of a mass in the abdomen. I can make little of the past history. The episodes of nausea and vomiting and of pain in the abdomen over the two years previous to entry seem rather typical of intestinal obstruction, but not much else. It is fortunate that this mass did cause pressure on the bladder and the ureter, because apparently that is the only reason the patient entered the hospital. The mass was said to occupy the entire lower abdomen but extended only 5 to 7 cm. above the umbilicus. By pelvic examination it was more on right side, and measured 8 cm. in diameter.

In attempting to determine the nature of such a mass, one can look at it from the anatomic point of view. Where could this mass have arisen? The first thing one thinks of is the uterus. This is ruled out because the pelvic examination showed a normal uterus. One next thinks of the ovary. That cannot be ruled out, and must be further considered. It may have been a mass attached in some way to the intestine. The positive guaiac test makes that seem somewhat likely. It might also have been an retroperitoneal mass of some form, lymphoma or fibroma or something of that nature. One must think of a bone tumor, but in the absence of any evidence of bone involvement one can safely rule that out. Under the circumstances, it seems a little unusual that they did not attempt a barium enema, because it would seem that more information could have been gathered from that than from anything else.

The next question one should decide is whether this was a malignant or a benign lesion. The cachexia, the weight loss, the pronounced anemia and perhaps the stony hardness of the mass, as well as the rapidity with which the symptoms developed, all lean strongly toward a malignant tumor. The consistency of the mass is rather less in favor of the usual retroperitoneal mass than it is of tumor of some other origin, although retroperitoneal masses may be extremely hard. Therefore, I should like to consider that it was an intra-peritoneal malignant tumor and that leads us back to a tumor of the ovary or of the intestine. I see no way of ruling out these possibilities in or out. The positive guaiac test in the stool makes one think that it might have been a tumor that had either eroded into the intestine or arisen from the intestine, causing some bleeding. On the other hand we already know that there had been a carcinoma of the breast, and one of the rather but not too uncommon sites of metastases

of carcinoma of the breast is to the ovary. A case came to my knowledge recently of a woman with carcinoma of the breast who had had the tumor removed several years before but had developed many bone metastases and had also developed large tumors in the pelvis. It was with some interest that the physician noticed a considerable regression of the bone metastases as the tumors of the pelvis became larger, and finally at autopsy it was found that the metastases from the breast to the ovaries had completely replaced the ovaries, thus causing physiologic castration; the regression of the bone symptoms was attributed to that. So I should like to make a diagnosis of carcinoma of the breast metastasizing to the ovaries.

DR. FREDERIC B. MAYO: Could this have been a Krukenberg tumor? If not, why not?

DR. HAMLIN: I should think that it could have been.

DR. BENJAMIN CASTLEMAN: From a primary cancer of the stomach?

DR. MAYO: Yes.

DR. HAMLIN: The description of the tumor does not exactly bring a Krukenberg tumor to mind.

DR. CASTLEMAN: Most of the Krukenberg tumors are bilateral.

CLINICAL DIAGNOSIS

Carcinoma of ovary?

Carcinoma of intestine?

DR. HAMLIN'S DIAGNOSIS

Metastatic carcinoma of ovary from previous carcinoma of breast.

ANATOMICAL DIAGNOSIS

Malignant lymphoma, clasmatoctytic type, of ileum, with extension into right ovary.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: It is not surprising that Dr. Hamlin was unable to decide where to place the tumor, — ovary or intestine, — because both were involved. The primary lesion was in a loop of ileum, the whole circumference of which for a distance of 11.5 cm. was replaced by a fleshy, smooth, pinkish-gray tumor, involving the entire wall and containing numerous areas of mucosal ulceration. The tumor in the ileum was attached to and had invaded the right ovary. Together they formed the mass in the right pelvis, and this was removed.

Microscopic examination showed it to be a very cellular tumor of the malignant lymphoma group, which we classified as belonging to the clasmatoctytic or reticulum-cell sarcoma type. One would have liked to compare this tumor with that of the original breast tumor. It is conceivable that the original tumor was a lymphoma, but it is more likely that the patient had two tumors.

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"EXPERT MEDICAL TESTIMONY"

A RECENT note in the April 1 issue of the *Journal of the American Medical Association* comments favorably on the attitude taken by the Minnesota State Medical Association, which three years ago appointed a committee on medical testimony to which could be referred instances in which physicians had given questionable testimony. This committee, after investigation and according to the facts, "may censure the physician, may publicize the circumstances of the particular case or may bring the matter to the attention of the state board of medical examiners for disciplinary action." A case is cited that had been investigated by the committee and referred to the board of medical

examiners; the testifying physician, having been adjudged to have given unjustified testimony, was censured.

So-called "expert medical testimony" as given in court has long been a just cause of embarrassment to physicians, who consider much of it to be a discredit to a generally honored profession. There are no undisputed rules by which qualification as an expert can be judged, and contradictory testimony is frequently given by presumably equally qualified physicians. Furthermore, neither the medical profession nor the legal profession has interested itself in this important problem to the point of actually seeking results.

The concluding paragraph of the note in the *Journal of the American Medical Association* is worth reprinting for its uncompromising clarity.

Next to saving life and giving aid to the sick and injured no greater responsibility devolves on the medical profession than giving testimony in court or elsewhere. The right of a physician to continue in the practice of medicine is measured not only by his professional competence as a physician but also by what he says and does as a physician.

In 1936 the Council of the Massachusetts Medical Society appointed the Committee to Consider Expert Testimony, thus anticipating the action of the Minnesota State Medical Association by five years. Unfortunately, although the Minnesota committee appears to be functioning in a spirited and effective fashion, the only fruit that this appointment has borne in eight long years has been an occasional meager report of progress. Meanwhile the battles of the "experts" continue.

SECONDARY STREPTOCOCCAL WOUND INFECTION

EPIDEMICS of secondary streptococcal infections of open wounds, such as burns, or of those following so-called "clean" operations are regularly experienced, particularly during the late fall, winter and early spring, by even the most expertly conducted surgical services. The usual reaction of the surgeon is to blame the sterile materials that he had used at operation, and the bacteriological laboratory is invariably swamped with requests for the cul-

turing of instruments, catgut-and dressings. Recent investigations, however, have proved that such material is rarely, if ever, the cause of the difficulty.

Since it is well known that during the winter months the incidence of throat infections due to beta-hemolytic streptococci and the number of apparently healthy persons who are carriers of these organisms are higher than they are in the summer months, it is logical to connect this prevalence with epidemics of secondary wound infection. The organisms may be seeded in several ways — by droplet infection at the time of operation and by dust or droplet infection when dressings are changed in the ward. The persistence of beta-hemolytic streptococci, as well as that of diphtheria bacilli, in dust has been demonstrated by a number of British investigators during the past five years. Garrod* has recently shown that the dust from wards where there are patients with streptococcal infections may contain these organisms in large numbers, particularly the dust near the beds of infected patients, that dust from poorly lighted areas is likelier to contain streptococci than is dust from sites on or close to windows and that virulent beta-hemolytic streptococci can persist in the dark in naturally infected dust for as long as one hundred and ninety-five days.

Prevention or elimination of secondary streptococcal wound infection calls for a meticulous routine. Efficient face masks should be worn by all members of the operating team. All personnel intimately concerned with operations or with the dressing of wounds should be tested weekly — or immediately if they develop a "cold" or sore throat — for the presence of beta-hemolytic streptococci in the nasopharynx, and they should be excused from these duties if the cultures are positive. If possible, all patients who develop streptococcal infections or who are carriers should be isolated. Ideally, the ward should be sunny. The floors should be oiled, and no sweeping or dusting should be permitted in the hour preceding the time when dressings are changed. No visitors should be admitted to the ward and activity within the ward should be restricted during the dressing period. Finally, all new dressings should be handled only with sterile instruments,

and these should be resterilized, or a new set used, for each patient. In the meantime, every surgeon should reconsider his technic from the point of view of decreasing the frequency of dressings. It has been shown, particularly in cases of burns, that, by using bulkier and more efficient dressings, they need not be changed oftener than once in two to four weeks, and in this way the danger of infection, as well as the amount of work, can be greatly reduced.

All these precautions undoubtedly cannot be taken at the present time, owing to the shortage of manpower. They offer, however, a goal to be attained, and many of them are relatively simple procedures whose adoption would accomplish much in lowering the incidence of secondary streptococcal wound infection.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

GRAVES — Word has been received of the death in the Pacific area of Lt. Commander Sidney C. Graves, U.S.N.R., formerly a prominent Boston gynecologist. His home was at 600 Brush Hill Road, Milton. He was in his forty-third year.

Dr. Graves received his degree from Harvard Medical School in 1929. He was assistant visiting surgeon at the Free Hospital for Women in Brookline and assistant in gynecology at the Harvard Medical School.

He was a fellow of the American Medical Association, a member of the American College of Surgeons, the New England Obstetrical and Gynecological Society and the Obstetrical Society of Boston and a diplomate of the American Board of Obstetrics and Gynecology.

His widow and three children survive.

HOWE — Harry N. Howe, M.D., of Greenfield, died May 11. He was in his seventy-third year.

Dr. Howe received his degree from Columbia University College of Physicians and Surgeons, New York, in 1899. He was president of the Franklin District Medical Society from 1916 to 1917. He was a member of the American Medical Association.

His widow survives.

MACDONALD — Frederick L. MacDonald, M.D., of Waltham, died May 24. He was in his sixty-sixth year.

Dr. MacDonald received his degree from the University of Vermont College of Medicine in 1907. He was the mayor of Waltham from 1934 to 1938. He was an instructor at Tufts College Medical School, on the staff of the Waltham Hospital and associated with the Massachusetts Eye and Ear Infirmary. He was a member of the American Medical Association.

A daughter and a granddaughter survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN

CLINIC	DATE	CLINIC CONSULTANT
Lowell	June 2	Albert H. Brewster
Salem	June 5	Paul W. Hugenberger
Haverhill	June 7	William T. Green
Brockton	June 8	George W. Van Gorder
Worcester	June 16	John W. O'Meara
Pittsfield	June 19	Frank A. Slowick
Springfield	June 21	Garry deN. Hough, Jr.
Fall River	June 26	Eugene A. McCarthy
Hyannis	June 27	Paul L. Norton

*Garrod L. P. Some observations on hospital dust. *Lancet* 1 245-247.

WAR ACTIVITIES

INDUSTRIAL HYGIENE

ETHYLENE CHLOROHYDRIN POISONING

A workman in a Los Angeles manufacturing plant, while cleaning trays upon which rubber strips were stored, used a petroleum hydrocarbon solvent of the kerosene range. The supply of the solvent being temporarily exhausted, the man then used anhydrous ethylene chlorohydrin for the same purpose. He was careful to wear impervious rubber gauntlets. The room was large and well ventilated, but he was exposed to the vapors of the solvent.

When, after two hours, the workman became very ill, he was taken to the dispensary and five hours later removed to the hospital, where he died, eleven hours after he first started to use the solvent. The man was sixty-one years of age and in excellent physical health up to the time of this illness. It was found on investigation that he had been exposed to an average concentration of vapor of about 1 mg. per liter of air (305 p.p.m.).

Six white mice were exposed to a similar atmosphere and all were ill in an hour, with a downhill course after two hours. Exposure was then ended, and four hours later one of the mice died while the others were extremely ill. In twenty-four hours, the 5 mice were again normal.

Autopsy of the deceased, evaluation of the exposure and duplication of the exposure in laboratory animals with similar pathological findings, led to the conclusion that death was due to anhydrous ethylene chlorohydrin, proving that the solvent is dangerous even in relatively low vapor concentration. — Reprinted from *Industrial Hygiene News Letter* (April, 1944).

CORRESPONDENCE

PHYSICIAN NEEDED FOR BOY SCOUT CAMP

To the Editor: Rhode Island, the littlest state in the Union, has the largest Boy Scout camp in New England. Eight hundred acres are maintained by the Narragansett Council, Boy Scouts of America, as "an Adventure Land forever," tenting between six hundred and seven hundred Boy Scouts a week during July and August.

Usually, these Yankee boys are healthy but occasionally one has an accident or is "upset" in some way or another. The Camp officials are desperately in need of a resident medical officer for the summer. In normal times they employ two men on the medical staff, but this year they have no idea where to secure such assistance. They have tried all the local hospitals, all the hospitals in Greater Boston, the Army and Navy units in and around Narragansett Bay, at Camp Devens and in First and Third Naval Districts, and refugee doctors — they have left no stones unturned.

They now turn to the *Journal* to air their problem over a larger area. Is there not some man who would enjoy eight or nine weeks with kids? There is a beautiful Health Lodge with a treatment room and waiting room, as well as a ward with eight beds, a laboratory and two isolation wards, all modernly equipped. The physician's living quarters are ample for a family.

A tired civilian physician, a discharged medical officer from some branch of the service or someone else ought to be anxious to "do a good turn" for these boys. Anyone who is interested or who has a thought or suggestion is asked to communicate with Mr. H. Cushman Anthony, Narragansett Council, Boy Scouts of America, 26 Custom House Street, Providence 3, Rhode Island, or phone GASpee 9618.

H. CUSHMAN ANTHONY

26 Custom House Street
Providence 3, Rhode Island

DEPRIVATION OF LICENSES

To the Editor: At a meeting of the Board of Registration in Medicine held on April 12 the Board voted to revoke the license of Dr. Samuel M. Weene, 241 Adams Street, Dorchester, Massachusetts, to practice medicine in the Commonwealth because of his conviction in court.

H. QUIMBY GALLUPE, M.D., Secretary
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held on April 12 the Board voted to revoke the license of Dr. William H. Briggs, Merrimac, Massachusetts, to practice medicine in the Commonwealth because of his conviction in court.

H. QUIMBY GALLUPE, M.D., Secretary
Board of Registration in Medicine

State House
Boston

DARIER'S DISEASE

To the Editor: Dr. Arthur M. Greenwood has just called to my attention an error on page 367 of the March 23 issue of the *Journal*.

The usual synonym of Darier's disease, at least in the dermatologic world, is keratosis follicularis, not pseudoxanthoma elasticum. It is true that both keratosis follicularis and pseudoxanthoma elasticum were studied by Darier. In the latter disease the name was given it by Darier in 1896, whereas keratosis follicularis was described independently in 1889 by Darier in France and Dr. J. C. White here in Boston. I have heard Dr. C. J. White say several times that the disease should have been named "White's disease" because of his father's contribution.

The description in the *Journal* fits the pseudoxanthoma elasticum all right but it is not what is commonly known as Darier's disease.

C. GUY LANF, M.D.

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Boston 15

Dr. Lane's letter was referred to Dr. Buck, whose reply is as follows:

To the Editor: I am forced to agree that, so far as all immediately available reference works are concerned, the eponym Darier's disease does indeed refer to a variety of keratosis follicularis.

My interest in any individual eponym begins when I hear it used for the first time. I must have been misled by hearing someone refer to a case of pseudoxanthoma elasticum as an example of Darier's disease. To that man and to myself Darier's disease meant pseudoxanthoma elasticum. Between us we must have created a new eponym.

Darier's conclusions regarding follicular keratosis may, I discover, be found in his article "De la psorospermose folliculaire végétante (On Vegetative Follicular Psorospermiosis)," which appeared in *Annales de dermatologie et de syphiligraphie* (10:597-612, 1889), with a translation from which I herewith make my apologies to the dermatologists:

There exists in man a group of cutaneous diseases that deserve the name of psorospermoses, since they result from the presence in the epidermis of parasites of the class Sporozoa . . .

This disease, which may be termed vegetative follicular psorospermiosis, should, in consideration of its etiology, be compared to Paget's disease and very probably to molluscum contagiosum.

ROBERT W. BUCK

5 Bay State Road
Boston 15

NOTICES

DIRECTORY OF MEDICAL SPECIALISTS

The third edition of the *Directory of Medical Specialists*, listing names and biographic data of all men certified by the fifteen American boards, is to be published early in 1945. Collection of biographic data of the diplomates certified since the 1942 edition, and revision of the older listings in that volume are now going forward rapidly. Diplomates are requested to make prompt return of notices regarding their biographies as soon as possible after receiving the proper forms from the publication office.

(Continued on page xi)

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MEDICAL SERVICE IN INDUSTRY*

DWIGHT O'HARA, M.D.†

BOSTON

THE title assigned to me suggests that there is a field in industry that medicine and surgery may enter and expand. Although this is undoubtedly true, the title might more appropriately read "Industry in Medical Service," thus indicating what is an even greater opportunity — that is, for industry to enter into and expand the field of medical service to its employees. I believe this because in the recent past and at the present time there are apparently more physicians ready and willing to enter industrial employment than there are industrial employers ready to engage them. The Committee on Industrial Health of the Massachusetts Medical Society has definitely found this to be so, even in this period of unprecedented industrial activity, for during the last year and a half it has received from physicians a dozen requests for industrial jobs for every one it has received from industrialists looking for physicians.

In this apparent discrepancy between supply and demand there are several noteworthy factors. In the first place, the supply pool, although it contains the names of several outstanding physicians and surgeons in the Commonwealth, is not a good random sample of the medical profession of the State. This is because the vigorous, well-trained physicians of today are apt to be too preoccupied with military and other services to be looking for work. In the second place, the industrialists are not generally aware of the potential usefulness of modern medical service in their business relations with their employees. They do not appreciate that the physiologic principles on which the upkeep of the human machine depends are as important as the mechanical principles on which they keep up their lathes and looms. In the third place, neither the physicians nor the industrialists generally know exactly what they are looking for, because industrial medicine is highly specialized as it has sometimes been repre-

sented to be; it needs further clarification as a specialty, if indeed it does not need to be reappraised as another form of the general practice of medicine.

There are now many types of industrial practice, and there are also many types of physicians engaged in it. They all have in common, however, certain interests that do not permit their straying as far from the fundamental principles and disciplines of medicine as many of the more highly organized specialists may. Within the last few years I have repeatedly heard candidates in Part III of the National Board Examinations request leniency or defiantly refuse to answer questions on the ground that they were not interested. This apathy was due to their intention to devote their talents to psychiatry, radiology or some other special field. They blandly assume that such interests release them from further responsibility in their wider profession. This attitude is sometimes found among third-year and fourth-year medical students, although they are usually discreet enough to keep it to themselves at that stage of their careers. The fact that such limitation of responsibility actually permits a specialist to command a larger income is one of the inconsistencies with which modern medicine has vested itself, and on account of which the cost of medical care has arisen in the large centers of population. The extent to which it has taken over the public's thinking about medicine is well known to those who have questioned the motives of the young men who now seek admission to our medical schools. In the most recent block of such young men whom I have questioned, for example, two out of twenty-one had already decided that they were going to become brain surgeons.

Of course everyone appreciates the technical advances that have paralleled this narrowing process. The primary point to be made in connection with it is that no such atrophy of medical and surgical interest or activity is compatible with the practice of industrial medicine. Certain industries have their

*Presented at the Year Session of the American College of Surgeons, Springfield, Massachusetts, March 20, 1944.
†Professor of preventive medicine, Tufts College Medical School, assistant physician, Boston City Hospital, physician-in-chief, Waltham Hospital.

own peculiar and often specialized problems, but the industrial physician must be ready to be all things to all men most of the time. He must be able to do the thing that general practitioners have always done so well: to decide quickly what is important and urgent, and to use pleasing and soothing devices for the rest. Although these soothing devices have frequently been amusing, they have admirably served their purpose, which is to get the patient out of the way so that the physician can get on with his work. In large plants with well-organized medical departments the industrial physician has greater resources than has the private practitioner, but it is just as necessary for him — or for someone on his staff — to get the employee back to his job as it is for the private physician to get the patient out of his office. My first thought about medical service in industry therefore is that it should be looked on, not as a new specialty in the conventional sense, but as a new application of the general practice of medicine.

The medical department of a large plant should and usually does provide a unit with which the family physician can co-operate with complete understanding and confidence. Such co-operation between industrial and family physicians is of the utmost importance in meeting the many problems now facing industry. Among these may be mentioned the breaking in of inexperienced workers, the adjustment of handicapped people to suitable jobs, the frequency rate of accidents, absenteeism following accidents or illness and the incidence of preventable illness. The medical department is interested in all these things, but they are closely and inexorably connected with housing standards, home environments, sickness in the family, previous illnesses and incapacities of workers, shopping, amusement and transportation facilities; in short, the things with which the family physician is traditionally familiar and concerning which he is often consulted. It may thus be said that there are at least two sectors of the home front of industrial health. The medical departments of large industries are universally anxious to correlate the medical command on these sectors, and may be counted on to come more than halfway in any movement toward unification of medical outlook. Most family physicians are now convinced that this is so; if they are not, they are lacking in experience. The private physician may now be expected to work for the welfare of his patient with the medical departments of the large plants as conscientiously as he does with the public-health authorities.

In the small plants on the other hand, where the opportunity to support a medical department is usually lacking, there is not apt to be an organized interpretation of medical viewpoints for the management, and the whole subject of medical service gets off to a poor start. Traumatic surgery is generally well cared for and is well followed up by the agents

of the insurance companies. Headaches and other minor complaints may be given symptomatic treatment, but there the service rests. The problem referred to in the preceding paragraph are almost unknown because they are not recognized, whereas absenteeism, which cannot escape recognition, becomes just "one of those things." There may be a nurse or two in attendance; attending physician and surgeons are generally called when needed and are usually paid on a fee basis. Representatives of such industries probably do not attend or do not know about the periodic meetings where industrial health is discussed. Obvious hazards are promptly corrected whenever attention is drawn to them, and it is not infrequently by a serious accident. It is true that the agents of these small plants can frequently point to excellent or even "perfect" safety scores, but such records perhaps depend on the relatively small number of employees involved or on the nonhazardous character of the particular trade that they ply. Of course many small industrial establishments are thoroughly healthful places in which to be employed. The chances are, however, that they are healthful places because someone not only has made an effort to make them so but also is attempting to keep them so.

The importance of these small plants in Massachusetts rests on the fact that their employees aggregate approximately three quarters of the men and women industrially employed within the Commonwealth. The problem is therefore large and complex, and because of the many small and diversified units into which it breaks down, it is a difficult problem. It is difficult from the employer's point of view because he cannot visualize a private medical department within his small plant any more than he can a private fire department. It is difficult from the physician's point of view because he cannot easily concentrate on the preventive aspects of an assignment that is really a very small part, and not at all an urgent one, of his total responsibility. Unless the employer or his physician can become enthusiastic about his admittedly little share of this big problem, not much progress can be made. If such progress is to be accomplished it is necessary to find an *enthusiast* — whether he is a manager, a physician, a foreman, a nurse or a janitor. He may be any intelligent person who will deliberately view a plant and ask himself about the possibilities of injury from fluids, fumes, dusts or metals. If his survey raises any suspicion that the worker's health is being undermined, the hunt is on. The physician who has this enthusiasm and interest is the ideal hunter. If he has practiced medicine successfully he will enjoy in a greater degree than do others, the confidence of those who know him, and as a physician he will have a natural knowledge of physiology on which he may build and through which he may be able to answer many primary questions. Indeed, the general practitioner may have

an approach that gives him fundamental advantages over other persons, even over specially trained industrial hygienists. No person who is not enthusiastic about the idea as a whole, however, will be likely to succeed in producing results.

There is a most useful group of people who are now organized and available in almost every community — the people who variously call themselves district, visiting or community-health nurses. They are in a particularly strategic position to promote industrial health in small plants, especially if the casually employed plant physician will give them the "green light." They are not expensive or intrusive; they are familiar and in daily touch with public-health regulations; they enjoy the confidence of the people and of the medical profession; a given slight encouragement by a few small plants they can afford to assign one of their staff to inform herself specifically in the principles of industrial hygiene. I have been much interested in watching the evolution of such a district nursing group in a city of 40,000 population with which I am familiar. They have successively trained different persons on their staff, so that in addition to what they call a "diabetic nurse" and a nutritionist they now have two members who have been trained in the elements of industrial hygiene. One of these nurses recently learned, almost surreptitiously, of a skin blemish that on tactful investigation was found to be part of a widespread epidemic of cutting-oil dermatitis among a group of women machinists whose thighs were exposed through absorbent overalls. Because their hands and faces were not involved these workers had not complained and had kept the condition of their legs to themselves. Medical advice led to proper protection and remedial measures, which promptly ended the trouble.

The nurse has traditionally held an intermediary position between the physician and his clientele; she can make or ruin him professionally almost as easily as his wife can make or ruin him socially. The nurse can as readily promote or neutralize industrial health; in the large and medium-sized plants she has already demonstrated her great value and has successfully promoted the health of the workers in many ways. In the small plants she must, however, be alert and resourceful; she must have a broad horizon, an active imagination and vigor if she is to keep herself from settling back into a soft corner,

where she has to knit and read while she waits for the opportunity to paint iodine on a hangnail. It seems that the small plant must be guarded against this leisurely sort of nursing routine, and for this reason the district nursing type of setup is extremely appealing. These district nurses have the added advantage that they are in close touch with the homes, the schools and the families of the men and women with whom they work. It is again the same advantage that the general practitioner enjoys — that of not being limited by the fence that surrounds the plant. The scope of industrial medicine, like that of preventive medicine, can have no such limit.

It is doubtful whether the managements of three or four different small plants could agree for long on the terms under which they might jointly employ an industrial nurse, but there is no doubt at all that they could all deal satisfactorily with an independent district-nursing organization. The independent organization, by working on an hourly basis, can adjust the service to the times that will meet the needs of each plant, thus relieving the plant managers of the vexing problem of deciding whether they should employ their nurses on full-time, half-time or quarter-time periods. It should appeal to the economic sense of businessmen to be able to buy only what they need. This is the best solution I have yet seen in operation for giving to small and moderate-sized industrial enterprises something that they can afford and that their employees are entitled to.

SUMMARY

Although single industries may expose their workers to special hazards, the practice of industrial medicine is a form of the general practice of medicine.

At the present time medical service is well organized in many of the large plants. Private practitioners should co-operate with the medical authorities of these plants as they do with public-health authorities.

Medical service in the small plants in Massachusetts is not well developed. It has been and can be developed by district-nursing groups in an efficient and economic manner. Private practitioners may well take the lead in this matter.

5 Bay State Road

THE CLINICAL SIGNIFICANCE OF BACTERIURIA IN PATIENTS
WITH SPINAL-CORD INJURIES*

DANIEL BADAL, M.D.,† DONALD MUNRO, M.D.,‡ AND MARION E. LAMB§

BOSTON

ALTHOUGH it has long been recognized that an infection of the genitourinary tract is one of the most prolific causes of death and disability in patients with spinal-cord injuries, we have been unable to find any data on the incidence of the different types of infecting agents, and in particular could discover nothing in regard to the clinical significance of a bacteriuria and the relation its presence has in such cases to the production of symptoms of cystitis, ureteritis or pyelitis. In the course of establishing the effectiveness of tidal drainage as a means of controlling infection of the genitourinary tract, it shortly became apparent that an effort must be made to differentiate a bacteriuria and an active infection of the tract. As integral parts of this problem the effectiveness of various urinary antiseptics had to be determined, the influence of an indwelling catheter on the prolongation of bacteriuria ascertained, the incidence of bacteriuria in normal uncatheterized persons settled, and finally a method developed by which the urine could be conveniently and accurately cultured and at the same time overgrowth of any one contaminant sufficient to mask the presence of others prevented. This paper presents our experience with these various problems.

METHOD OF CULTURE

It was obvious that before any such investigation could be undertaken a proper method of culture must be developed. Moreover, to be significant the urine to be cultured had to be bladder urine uncontaminated by passage through the urethra. It was evident that to meet this requirement catheterization would be necessary. Moreover, some method must be adopted to minimize the effect of the contamination of the bladder urine by the transference of urethral bacteria on the catheter as it was inserted. The method that was finally evolved and that has proved satisfactory for the last eight years follows. It is reliable, dependable and accurate. The cultured plates are easy to read and are not overgrown by the more prolific bacteria.

After washing the external meatus with soap and water a new sterilized catheter is inserted in the bladder. The use of a new catheter decreases the chances of contamination slightly and is preferable

but not essential. Catheters that have been in use so long a time as to have become encrusted with urinary salts should not be employed. The bladder is emptied and irrigated gently with a sterile 0.5 per cent solution of acetic acid, which is then removed. The catheter is fastened in place and clamped off, and the bladder is allowed to fill from the kidneys for two hours. At the end of this time the catheter is opened and 10 cc. of urine is allowed to wash through the catheter, which is then closed off again. The outer wall of the catheter is sterilized by painting the area between the meatus and the clamp with full-strength tincture of iodine. This is allowed to dry, a sterile hypodermic needle attached to a sterile syringe is plunged through this area into the lumen of the catheter, and urine is withdrawn therefrom into the syringe. One drop of this urine is placed on a blood agar plate and spread over half the plate with a sterile loop. The loop is then resterilized and the other half of the plate is subcultured from the urine that has been spread over the first half. The ideal way is to plate the urine at the patient's bed with due care to prevent contamination, but if this cannot be done the syringe and needle should be carried at once to the bacteriological laboratory and the plating carried out there. Any delay in making the culture alters the relative amounts of the various bacteria in the urine and leads to confusing overgrowths on the plate. An eosin-methylene blue plate and blood broth may be used. We have not made anaerobic cultures.

Urine cultures have been made by this method on 53 out of 169 cases with all levels of spinal-cord and cauda-equina injuries. Five hundred and seventy-eight cultures have been examined (Table 1). Table 2 shows the number of cultures per patient, and Table 3 gives certain data relative to the

TABLE 1. Total Number of Urinary Cultures.

TYPE OF SPINAL INJURY	NO. OF CASES CULTURED	NO. OF CASES NOT CULTURED	TOTAL CASES	TOTAL CULTURES
Cervical:				
Living	24	31	55	311
Dead	4	42	46	24
Thoracolumbar:				
Living	8	10	18	118
Dead	6	17	23	62
Cauda-equina:				
Living	11	14	25	63
Dead	0	2	2	0
Totals	53	116	169	578

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‡Assistant professor in neurosurgery, Harvard Medical School; associate surgeon, Boston University School of Medicine.
§Bacteriologist, Boston City Hospital.

first culture made and to cultures made within twenty-four and forty-eight hours after the injury; as well as the total number of various bacteria

grouped according to the class of case. The first culture made in each patient showed a single type of organism in only 20 cases. There was no growth in 27. Table 4 shows the total number of cases in which the different kinds of bacteria were cultured. It is apparent that *Proteus vulgaris*, *Esche-*

there were too many uncontrollable factors to make them suitable subjects. In addition to plating 1 drop of urine, cultures in blood broth were made of 1 cc. and 5 cc. of urine in order not to miss the more dilute concentrations of bacteria. Growth on the plates was reported as follows:

TABLE 2. Number of Urinary Cultures Per Patient.

TYPE OF SPINAL INJURY	1	2	3	4	5	6-10	11-20	21-30	31-40	41-50	OVER 50	TOTAL CULTURES
Cervical												
Living	1	5	1	2	1	5	5	0	1	2	1	24
Dead	2	0	0	0	0	1	1	0	0	0	0	4
Thoracolumbar:												
Living	2	0	0	1	1	1	1	0	0	0	1	8
Dead	1	0	0	0	0	1	1	0	1	0	0	6
Cauda-equina:												
Living	2	1	1	2	1	2	2	0	0	0	0	11
Dead	0	0	0	0	0	0	0	0	0	0	0	0
Totals	8	7	2	6	3	10	10	1	2	2	2	53

Esche. coli, alpha-hemolytic streptococci, enterococci and staphylococci are the significant bacteria. It should also be noted that although proteus and colon bacilli predominated in the cultures, alpha-hemolytic streptococci and enterococci were present at one time or another in the bladder of as many patients as showed the former two bacteria. It also appears probable in the light of this

four to ten colonies, +, the most profuse growth +++++, with ++ and +++ in intermediate types of growth. All the cases that showed positive cultures in 1 drop of urine also showed positive cultures in 1-cc. and 5-cc. amounts. Diphtheroids were grown six times in 5 cc. of urine only. They appeared alone five times and in combination with *Staphylococcus albus* once. When

TABLE 3. Results of Urinary Cultures.

TABLE 3. Results of Urinary Cultures.										
ORGANISM	GROWTH			TYPE OF SPINAL INJURY						TOTAL CULTURES
	FIRST CULTURE	24 HR AFTER INJURY	48 HR AFTER INJURY	CERVICAL		THORACO-LUMBAR		CAUDA-EQUINAL		
				Living	Dead	Living	Dead	Living	Dead	
<i>P. vulgaris</i>	4	0	0	106	4	62	44	33	0	249
<i>Es. coli</i>	4	0	0	160	11	44	32	35	0	282
<i>Enterococci</i>	1	0	0	37	8	30	7	9	0	91
Alpha hemolytic streptococci ..	2	1	0	78	8	20	17	26	0	149
Staphylococci ..	2	0	0	67	13	37	7	20	0	144
Other streptococci ..	0	0	0	6	1	3	0	3	0	13
<i>Ps. pyocyaneus</i>	0	0	0	13	1	4	4	3	0	25
Diphtheroids	0	0	0	11	0	3	4	2	0	20
Mycetozoans	0	0	0	40	2	16	9	9	0	76
No growth	7	0	0	27	1	0	1	1	0	30
	27	3	2							

and the figures cited above that in this type of case *Pseudomonas pyocyaneus*, nonhemolyzing streptococci, a miscellaneous group of bacteria and possibly diphtheroids may well be contaminants of the various cultures rather than true inhabitants of the urethra or the bladder urine.

CONTROLS

In an endeavor to determine the incidence of bacteriuria among normal persons, 50 men were selected for urinary culture (Table 5). Before selection a careful history was taken and a thorough physical examination was made. Only those patients who had a history of never having had any genitourinary disease or injury and whose condition at the time of examination had no relation to the genitourinary tract were included. No women were examined because it was believed that

they appeared alone there was no other growth in any dilution. *Staph. albus* was grown alone once and in combination with an alpha-hemolytic streptococcus once; and an alpha-hemolytic streptococcus was grown alone twice, but in 1 cc. and 5 cc. of urine only. When present at all, *Staph. albus* showed only 1 colony per plate three out of four times and a + growth once. *Esch. coli* was present in ++ amount once, as were alpha-hemolytic streptococci in + amount; *Staph. citreus* showed only one colony per plate once.

Clinical evidence of bacteriuria, with or without evidence of infection in the form of a rise in temperature and leukocytes in the urine, was investigated in this control group. No patient had an abnormal temperature. In looking for leukocytes 10 cc. of urine was collected at the time of the culture and examined in a fresh state. The specimen was slowly centrifuged for two minutes and the un-

point where a dangerous illness developed. In certain cases the bacteria could not be killed even *in vitro* by the drugs. Salvarsan was tried intravenously in another group of patients suffering from what were believed from the descriptions in the literature to be susceptible infections but was a failure in every case. Urotropin by mouth was not tried. Hand irrigation of the bladder at four-to-twelve hour intervals was also practiced using suspensions of sulfanilamide, sulfathiazole and sulfadiazine, and 1:500 and 1:300 dilutions of an aqueous iodine solution (Lugol's). The sulfonamides were complete failures. If the iodine solution was instilled into the bladder and left there for five minutes, it could be demonstrated that the iodine was all absorbed, and indeed in one case symptoms of iodism appeared. The urine, however, was not sterilized. Daily irrigations were no more successful. By this time certain of the earlier patients who had had pyelitis and bacteriuria during their stay in the hospital but whose bladders had returned to normal before their discharge had had urine cultures made on them at various intervals after permanent removal of the inlying catheter. In every case except 2, and in spite of the failure of previous medication, these patients' urines became sterile without any further treatment other than the removal of the catheter, and all remained so. Such end results have been reported elsewhere by one of us,¹ and are introduced here only to emphasize the failure of these attempts to sterilize the urine when the inlying catheter remains in the bladder.

At about the time of these experiments MacNeill and Bowler³ published their modification of the tidal-drainage apparatus. This provided efficient bladder irrigation. It was also drawn to our attention that potassium permanganate—which was the irrigating solution then in use—was alkaline and therefore not suitable for control of the bacteria that flourished in an alkaline urine. The tidal-drainage apparatus was therefore redesigned and a 0.5 per cent solution of acetic acid was substituted for the permanganate. The culturable bacteria were reduced in numbers, and with a stronger solution of acetic acid the urine could be rendered mildly acid, but it could not be sterilized. Certain urines that tended to throw down phosphate crystals could be made clearer, but the bacteria were still present and remained until the inlying catheter was withdrawn, after which, if the bladder was either normal or of reflex type, they disappeared without anything further being done. Before this conclusion was reached, aqueous iodine, all strengths of acetic acid solution up to 5 per cent and suspensions of sulfathiazole and sulfadiazine had been used without any effect except to produce salivation and mild iodism in 2 patients. No urines were sterilized by any of these solutions. Clinical evidence of pyelitis and cystitis dropped

off sharply, however, because of the greater efficiency of the tidal-drainage apparatus. The most significant findings of all this investigation, so far as the bacteriology was concerned, were two. One was that male urethras that are deprived by presence of an inlying catheter of the irrigation and mechanical cleansing they ordinarily receive whenever the bladder is normally emptied are a constant source, particularly at every fresh catheterization, of reinfection of the bladder urine. The other is that the tidal-drainage apparatus itself reinfests the bladder urine if it is not completely dismantled, cleaned and sterilized once a week.

For the last two years no attempt has been made in this clinic to alter the bacteriuria that is always present in association with the use of tidal drainage in patients with a spinal-cord injury. All one of such patients who have left the hospital during this period have had sterile urines provided the indwelling catheter is no longer in place. The genitourinary tracts have been otherwise normal and the function has been appropriate to the lesion in every case. With the use of the present day tidal-drainage apparatus as further modified by Stewart⁴ as well as by Cone and Bridgers, insistence on weekly cystometrograms, the use of small catheters and the avoidance of all instrumentation of the bladder, the occurrence of urethritis, ureteritis and cystitis has ceased to be a significant problem except in the presence of a bladder stone. When any such infections occurred, they have been brought under control in every case without the use of drugs by means of the tidal drainage and by the proper adjustment of the tidal-drainage apparatus and the administration of large quantities (5000 cc. every twenty-four hours) of fluid by mouth, through a stomach tube or intravenously. A renal stone developed in 1 case, a bladder stone in 2. All these stones were removed surgically. We are therefore convinced that administration of the sulfonamides or any of the other so-called "urinary antiseptics" by mouth as an irrigating fluid in the bladder cannot control the bacteriuria that always accompanies an inlying catheter as used in the treatment of the tidal drainage of patients with spinal-cord injury. Moreover, we have satisfied ourselves that bacteriuria is harmless and disappears with permanent withdrawal of the catheter, and that pyelitis, ureteritis or cystitis does not develop in the course of treating such a patient, such an infection promptly clears up following either the removal of any stone that may be present or adjustment of the apparatus and the ingestion of adequate fluids.

SUMMARY AND CONCLUSIONS

A satisfactory method of making a urine culture is described.

asymptomatic bacteriuria may be present in a healthy, active person without his knowledge and without the production of symptoms.

The presence of an indwelling urethral catheter is always accompanied by bacteriuria by the end of twenty-two hours.

Patients with spinal-cord injuries who are treated with tidal drainage have an alkaline urine that is acidified.

Isolation of the urinary tract as distinct from bacteriuria in such patients is best recognized by bacteriologic signs. These are the onset and progress of the disease, the study of the urine and a sudden rise in the temperature, usually accompanied by a

personal experience sterilization of the urine in the case of an indwelling catheter used as part of the drainage apparatus in treating patients with spinal-cord injuries has been impossible except by withdrawal of the catheter, and is unnecessary provided the latest-type apparatus is used and is properly adjusted to the bladder it is serving. Isolation of the urinary tract as evidenced by the symptoms and signs of pyelitis, ureteritis and bacteriuria in a patient with a spinal-cord injury who is treated by tidal drainage is best controlled by adjustment of the apparatus, bed rest and administration of large amounts of fluid, usually by mouth.

Patients who have had a spinal-cord injury and recover to be discharged from the hospital can expect to have a normal genitourinary tract with normal function and without bacteriuria unless they have had a transection of the cord, a renal or bladder stone, a draining periurethral abscess or a lesion that has produced permanent physiologic or anatomic denervation of the bladder.

If such a patient has had a transected spinal cord, he can expect a reflex bladder without bacteriuria and without the need for an indwelling catheter under ordinary circumstances.

If such a patient has had a physiologic or anatomic denervation of the bladder as the result of injury, he can expect a shrunken, useless bladder with bacteriuria and probably recurrent bouts of pyelitis.

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TUBERCULOSIS OF THE LOWER LOBE

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THE lower lobe of the lung as the origin of reinfection tuberculosis has been the subject of discussion from time to time in the past. It has never been treated as an entity in textbooks and in all probability does not deserve to be. However, because of its comparative infrequency in routine admissions to sanatoriums and consequently its much rarer appearance in general practice, there has been a tendency on the part of physicians to ignore its existence. Within the last few years three noteworthy clinical studies have been reported, calling attention once again to this syndrome, its possible pathogenesis and the other factors that are peculiar to manifest tuberculous disease in this area.¹⁻³

True basal lesions—that is, those found just above the diaphragm—are extremely rare, but tuberculous lesions located in the upper portion of the lower lobe are not infrequently observed. In fact, as far back as 1888 the latter location was

commented on by Fowler,⁴ who wrote that the apex of the lower lobe was second in vulnerability to the extreme apex itself. Since then others have shown that this site is not an unusual location for early cavities.

A study of the literature shows that the reported incidence of adult-type or reinfection-type tuberculosis of the lower lobe varies considerably. It ranges from 0.003 per cent of sanatorium admissions, as recorded by Reisner,¹ to 5.6 per cent for men and 10.0 per cent for women, as reported by Viswanathan.⁵ In this country it varies between 0.5 and 4.0 per cent of sanatorium admissions, with the latter figure representative of the incidence in female patients.⁶⁻¹¹ It is generally accepted that the frequency is greater among women than among men, on the right side as compared with the left and in the younger age groups as compared with the older ones,³ and that race and nationality seem to play no part.

The material available for this report was accumulated over a six-year period (1931 to 1937) in which

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some 700 admissions occurred at the Norfolk County Sanatorium. The 14 cases represent 2 per cent of all admissions during this period.

In most of the available reports the authors state that their series consist of cases in which the manifest clinical tuberculosis is believed to have begun in the lower lobe. Many writers add that some of these cases have small nodular or fibrotic lesions in one of the apices, but because the presenting and predominant disease is in the lower lobe, they consider the other lesions inactive or obsolete and hence of no consequence. The material gathered for this report deals with the same type of case, but the presence of contralateral or ipsilateral involvement outside the lower lobe has been recognized

in one or the other apex. Although this is a small series and thus not properly suited for statistical use, an analysis of these two groups presents data that are deemed worthy of consideration.

Three cases were not included in this series. One was that of a granite worker over sixty years of age who had unquestionable evidence of silicosis and in whom a tuberculous cavity was first noted in the left lower lobe. In a series of over 75 cases of silicosis and tuberculosis there were 3 in which the tuberculous cavity of infiltrate seemed to begin in the right middle lobe. In such cases, where two diseases resemble each other closely, it is difficult to determine in which locality the tuberculous process first becomes clinically manifest, although the major

TABLE 1. Summary of Data.

CASE No.	SEX	AGE yr.	CONTACT WITH TUBERCULOSIS	SIDE AFFECTED	REACTION OF SPUTUM	TYPE OF ONSET	COMPLICATION	TREATMENT	RESULT (1943)
PURE TYPE									
1	M	19	Mother and 2 siblings	Left	Positive	Acute	None	Pneumothorax	Disease arrested (10 yr.)
2	F	16	Father	Right	Positive	Acute	None	Pneumothorax and phrenicectomy	Disease arrested (3 yr.)
3	F	17	Brother	Left	Positive	Acute	None	Pneumothorax	Disease arrested (3 yr.)
4	F	19	Mother	Right	Positive (gastric lavage)	Chronic	None	Pneumothorax and phrenicectomy	Disease arrested (4 yr.)
5	F	17	Sister	Right	Positive	Acute	Spread to opposite side	Pneumothorax and phrenicectomy	Patient failing; positive sputum.
6	F	19	Sister	Left	Positive	Acute	None	Bed rest	Disease arrested
7	M	23	None elicited	Right	Positive	Acute	None	Pneumothorax	Disease arrested
8	F	22	Brother	Right	Positive	Acute	Tuberculosis, enteritis	Pneumothorax	Death
IMPURE TYPE									
9	F	29		Right	Positive	Chronic	None	Pneumothorax and thoracoplasty	Disease arrested
10	F	33		Right	Positive	Chronic	None	Phrenicectomy and pneumothorax	Patient refused thoracoplasty; positive sputum.
11	F	37		Right	Positive	Chronic	None	Pneumothorax and pneumolysis	Disease arrested
12	F	26		Right	Positive	Chronic	None	Pneumothorax and phrenicectomy	Disease present; negative sputum.
13	F	23		Right	Positive	Chronic	None	Pneumothorax	Disease arrested; recurrence on opposite side (6 yr. later)
14	F	37		Right	Positive	Chronic	None	Pneumothorax and pneumolysis	Negative sputum after pneumothorax

and has been made the basis for dividing the cases into two groups (Table 1). A new classification is not offered, but for the purposes of study the cases have been arbitrarily divided into these two groups and the terms described below have been applied. Furthermore, it is fully realized that x-ray studies are too crude for absolute differentiation of the two groups, but they are justified by the results of the analysis. By making this distinction, a unique approach not hitherto reported is attempted and the results of analysis seem to warrant reporting.

In the first group, designated as "pure," are placed 8 cases in which the x-ray appearance of the lesion was limited entirely to the lower lobe with no visible evidence of obsolete, nodular or fibrotic lesions elsewhere in the lungs. In the second group, designated as "impure," are placed 6 cases in which in addition to the predominant lower-lobe lesions nodular or fibrotic disease, such as described above, was found

of silicotic patients develop phthisis in the upper lobes in the same proportion as do those with tuberculosis uncomplicated by silicosis.

The second case was that of a seventy-five-year-old woman who had bronchiectasis of the lower lobe of twenty years' duration. A sputum positive for tubercle bacilli was demonstrated once in a series of more than fifty examinations. After death from congestive heart failure, autopsy disclosed considerable bronchiectasis of the right lower lobe, a just beyond the wall of one of the smaller bronchi a caseous tubercle 1 cm. in diameter was noted. It is difficult to classify this case. The patient may not have active tuberculosis in the accepted sense. A logical explanation is that before death there was softening of an old tuberculous focus, perhaps owing to a bronchiectatic abscess or low-grade pneumonia with consequent shedding of a few bacilli in the sputum.

The third case was that of a male diabetic patient forty-four years of age who had a small lesion in the apex on the right side. Since the evidence for a lesion of the middle or lower lobe was not clear, this case has been omitted.

SYMPTOMATOLOGY

A study of the onset reveals that the cases in the present series are roughly divided into the acute and chronic types. The former, generally associated with the pure type, simulated the onset of pneumonia, whereas the latter was common to the impure type and was most frequently diagnosed as bronchitis or bronchiectasis. Of themselves, no symptoms were found to be pathognomonic of lower-lobe tuberculosis. Sokoloff,¹² however, points out that in his series a distinction in the symptomatology could be noted by early onset of night sweats, which in addition usually affected a limited part of the body—that is, the neck, shoulders or head. He also reported an afternoon fatigue that disappeared with rest.

Analysis of this series (Table 2), shows distinct differences with respect to age, sex, side affected and type of onset. As regards the history of tuber-

reported studies. Available statistics reveal that more girls than boys develop manifest tuberculosis during adolescence. Thus, one expects a greater percentage of teen-age girls than of teen-age boys in a sanatorium, and hence a greater opportunity for encountering lower-lobe disease among females than among males. This does not, however, explain why there are not more cases of lower-lobe tuberculosis among men between twenty-five and thirty-five years of age, in which age group the male incidence of tuberculosis is at its highest. Some other explanation than that of age must be sought to explain the localization of basal tuberculosis.

The right side was involved in all the impure cases and in 5 (62 per cent) of the 8 pure cases. This finding is in accord with that of most writers. Eleven of the 12 women had the lesion on the right; in both the men they were equally distributed.

PATHOGENESIS

Two mechanisms regarding the pathogenesis of the pure group suggest themselves. According to the first of these, the caseous-pneumonic lesion is the result of a bronchiogenic or hematogenous spread from the lymph-node component of the primary infection and the lesion, which is usually situated in the upper lobes, has by chance involved the lower lobe. According to the second mechanism, there is direct extension from the parenchymal component of the primary complex, which is oftenest found in the lower lobe on the right side. Sweany¹³ has shown that such a process actually occurs in adolescents or young adults who acquire their primary infection during adolescence. The course in these cases is, however, generally rapid and fulminating. The present series includes no case of this type, with the possible exception of Case 8, in which death from tuberculous enteritis occurred.

The impure cases appear to offer more consistent findings. The universal localization in the lower lobe on the right side in women is the outstanding finding. This is best explained on the basis of a theory developed by Reiser.¹ This theory presupposes an area of marked limitation of motion in the lung, which Tendeloo and Macklin¹⁴ have termed the superoretrocardiac area. Roughly, the area is paravertebral and corresponds to the usual location of the apex of the lower lobe. This theory has been worked out in the following manner. The diaphragm plays an important role in the expansion of the lower lobe and the posterior portion of the upper lobe, whereas the costal movements are largely responsible for the expansion of the middle lobe and the anterior part of the upper lobe. In general, therefore, it can be postulated that the effectiveness of diaphragmatic action progressively decreases posteriorly and superiorly and that minimal action is obtained at the area corresponding to the apex of the lower lobe. Men are known to be predominately diaphragmatic breathers,

TABLE 2. Analysis of Series.

FACTOR	PURE TYPE	IMPURE TYPE
Sex	6 females; 2 males	6 females
Age	16-23 yrs., average 19 yr.	23-37 yrs., average 31 yr.
Side affected	5 right; 3 left	6 right
Tubercle bacilli in sputum	All	All
Type of onset	7 acute; 1 chronic	All chronic

culous contact, in the pure group there was a strong family history of tuberculosis and intimate contact, suggesting that these patients had received large and frequent dosages of tubercle bacilli in the past. The majority of them had been separated from their original contacts for many years. This is a not frequent history in tuberculosis of the upper lobe. In the impure group there was no history of tuberculosis contact, familial or otherwise. This suggests that a small apical lesion is acquired after many years of sporadic or chance infection and becomes arrested or quiescent. At some time later in life, perhaps during an intercurrent respiratory infection, the bacilli are set free from this old focus, drain down the right bronchus and are localized in the area of alterability (described below), where they thrive and ultimately cause caseation, slough and cavitation. With the development of the cavity, the symptoms bring the lesion to the attention of the patient, who seeks medical advice. The impure type is probably not true lower-lobe disease but what could be more properly termed metastatic lower-lobe tuberculosis. For this group a hypothesis has been advanced to explain the predisposition for the right side and the lower lobe.

It is difficult to explain the numerical preponderance of female over male cases in this and other

whereas women are costal breathers; consequently, in the latter normal respiration demands little diaphragmatic excursion, with the result that the lower lobe, particularly its upper portion, is poorly ventilated. One can therefore account for a region in the lung that is relatively inert, poorly aerated and in all probability vulnerable to infection. Furthermore, the right side of the diaphragm is more elevated than the left, owing to the underlying liver, and is in consequence liable to a somewhat lessened excursion. This is particularly so in women, as shown by fluoroscopic examinations of the chest. Reisner¹ adds that the right main bronchus comes off the trachea at a lower angle than does the left main bronchus, and in consequence any spreading bronchiogenic infection more naturally drains to the right than to the left side, thereby coming to rest in this vulnerable area. Since the majority of writers have noted the marked preponderance of tuberculosis in the right lower lobe in women, this theory seems to explain their predilection for lower-lobe disease as compared to that of men.

Medlar and Sasano,¹⁵ working with various strains of tubercle bacilli inoculated intravenously in vaccinated rabbits, noted that cavitating lesions were localized in the dorsal and posterior parts of the lung, which are in the superior portion of the rabbit in the usual position of rest, whereas the lesions in the anterior and ventral portion had cleared. Further experiments, in which the rabbits could be kept in a given position for over half the day, over a long period of time, resulted in earlier death, but examinations revealed a localization of the tuberculosis in the highest part of the lung. These authors note an analogy between this tendency to superior localization and the apical or subapical involvement in the human lung.

Medlar and Sasano frankly admit they do not know why the lesions localized as they did, since there is admittedly no peculiar anatomic structure of the lung that lends itself to progressive infection. Also, an alteration of the lung occurs with a change of posture, since emphysema develops in the rabbit's lungs if it is kept in an upright position over a given period of time.

From these studies, it was obvious that neither inhalation (the natural route) nor allergy with subsequent reinfection is of prime importance in the determination of the localization of the progressive cavitating tuberculous lesion.

It is common knowledge that a considerable proportion of spreads to the lower two thirds of the human lung resolve completely, and when they do not, this is probably due to an overwhelming infection or to extreme virulence of the germ. A progressive basilar infection is therefore always of grave import, especially in the absence of apical or subapical involvement. Medlar and Sasano conclude that higher portions of the lung field are less resistant to tuberculous infection than are the lower

portions, and that to obtain localizing cavitating lesions it is necessary to have a certain balance between the virulence and dosage of the tubercle bacilli and the resistance of the host, together with a localizing of the tubercle bacilli in certain areas of lung parenchyma; that allergy alters the tissues only so far as the response is more vigorous or prompt; and that this alteration is but one factor that may lead to a localizing cavitating lesion. The factor of greatest importance seems to be the establishment of a certain balance between host and parasite.

DIAGNOSIS

Lateral as well as conventional x-ray films are necessary before a topographical diagnosis of lower-lobe disease can be entertained. The diagnosis of tuberculosis should not be made unless a positive sputum (or gastric lavage) is obtained. As will be noted, this was demonstrated in every case in the series. This does not mean that a positive sputum will be obtained in every case of lower-lobe tuberculosis when first seen. On the contrary, it may not be possible to obtain one in the first few days or even weeks after onset, especially in the pure type. This is also true of the proliferative or exudative type, which resembles a low-grade pneumonitis persisting over four to six weeks, and in which a strong contact history of tuberculosis can be elicited. In such cases it may take months of sputum and gastric examinations before tubercle bacilli are found.^{16,17} Thus, roentgenologically speaking, lower-lobe lesions differ from apical ones in that in the latter a diagnosis of tuberculosis can often be made without a positive sputum, whereas in the former a positive sputum is essential.

In the differential diagnosis another lesion that may cause confusion is an active apical tuberculous lesion in association with a unilateral or bilateral basilar nonspecific bronchiectasis. Although this is a rare combination, it is important that the distinction be made, since the principles of treatment for each condition differ markedly. Bronchography and if necessary bronchoscopy should be carried out if the double condition is suspected. A lead to the diagnosis is the copious quantity of sputum, out of all proportion to the size and number of tuberculous cavities present, as well as the small degree of parenchymal involvement in the face of a positive sputum.

Of particular interest at present are the atypical pneumonias, most frequently basilar in distribution and requiring three to six weeks for resolution. They are, however, usually migratory and bilateral, which differentiates them from tuberculosis by the changing signs and the sequence of events. Serial chest roentgenograms soon rule out this condition. In fact, it cannot be emphasized enough that a single positive x-ray film of the chest is often not only misleading but dangerous.¹⁸ Besides the atypical

pneumonias, one must bear in mind the delayed type of resolving lobar pneumonia due to a pneumococcus, particularly since the right lower lobe is often involved.¹⁹ The time interval required for resolution and the absence of residue differentiate these two conditions. It also helps to differentiate basal pneumonias complicating minimal or obsolete apical tuberculosis from tuberculous spreads.

Lung abscess should not be confused with lower-lobe tuberculosis since most of these abscesses follow surgical procedures, and the others can be ruled out by repeated sputum examinations. The sudden onset, the typical pus and the physical signs also aid in the differentiation.

As for the pulmonary mycoses, coccidioidal infections are a problem peculiar to Southern California and to the San Joaquin Valley in particular. Other fungus infections of the lung can be diagnosed from sputum cultures and the usual bilateral nature of the disease.

Neoplasm of the bronchus may give difficulty if associated with tubercle bacilli in the sputum. I have seen 2 such cases, both of which occurred in men of fifty and over. Age and sex therefore help in differentiating the two conditions. Bronchoscopy usually makes the proper diagnosis possible.

To reiterate, the commonest error is to confuse the pure type with pneumonia and to treat it as such for many weeks. This can largely be avoided if an inquiry concerning a history of tuberculous contact is made and appropriate sputum studies, together with serial x-ray examinations, are carried out in all young people acutely ill with pneumonitis.

The impure type rarely gives any trouble, because the associated evidence of ipsilateral or contralateral apical nodular or fibrotic involvement is practically pathognomonic of tuberculosis. The chest roentgenogram indicates the diagnosis, and studies of the sputum invariably confirm it.

PROGNOSIS AND TREATMENT

The prognosis of lower-lobe tuberculosis does not differ from that of disease elsewhere in the lung, depending in large part on the type of disease present. Productive or proliferative disease has a slow and benign course, whereas caseous pneumonic disease has a high morbidity and mortality if not actively treated. All the cases in the present series were either those of acute caseous pneumonia or of its sequela, the fibrocavernous type.

It is interesting to note that many of the earlier writers give an extremely poor prognosis to all basal lesions. In fact, Dunham and Norton²⁰ were so impressed by the typical course of these lesions that they called all progressive caseous pneumonic disease, whether or not found in the lower lobe, the basal type. They had a large percentage of Negroes in their series. Today, it is thought that the prog-

nosis largely depends on the type of lesion and not on its location.

The principles of treatment for lower-lobe tuberculosis do not differ from those for other lesions and in consequence open cavities must be closed as quickly as feasible. This means that in the acute pneumonic variety, before artificial pneumothorax can be initiated, bed rest is advised until caseation, sloughing and evacuation of the cavity contents have been accomplished and the surrounding pneumonitis has subsided. Not only are complications avoided by this regimen, but also on occasion one may be rewarded by a closed cavity and conversion of sputum, thus saving the patient years of prolonged collapse therapy. Except for one case, the entire series required a dynamic approach for ultimate control.

In the past, lower-lobe lesions have been a strong indication for interruption of the phrenic nerve, but it has been my experience, as well as that of many other workers, that there is little benefit to be derived from the procedure per se, especially where it is the sole means of providing rest and collapse. In fact, in the presence of acute disease it may constitute a distinct danger, since it may cause atelectasis of the lower lobe. Again, with diaphragmatic paralysis thoracoplasty may be dangerous until the function of the diaphragm returns, since atelectasis has been seen in the presence of an elevated diaphragm following such surgery. It seems certain that the only place for phrenic-nerve paralysis is as an adjunct to an existing pneumothorax or thoracoplasty.

In this series of cases, artificial pneumothorax was somewhat more successful in the pure group than in the impure, owing in large part to the paucity or even absence of adhesions in the former, which allows for more adequate collapse of the underlying lung without the necessity of supplementary procedures. This fact may be presented as presumptive evidence that the onset of the impure type is insidious and the disease of long standing. It is in these cases that one encounters the largest number of adhesions, not only about the base but around the apex.

Extrapleural pneumothorax has no place in this form of disease. Intrapleural pneumolysis should be used as a supplementary procedure to sever adhesions that are preventing the satisfactory collapse of the lung. Thoracoplasty has its place but should not be attempted until after long trial of bed rest and minor collapse procedures. When performed, it generally requires the resection of eleven ribs and often anterior section before closure of the cavity is obtained. More recently the tendency has been to make a bronchoscopic examination of all cases for bronchial lesions, since collapse therapy is of little value in those with ulceration. Lobectomy and pneumonectomy are procedures choice of in

certain of these cases, with complete extirpation of the disease as a possibility.²¹

SUMMARY

An analysis of tuberculous lesions in the lower lobe of the lung is made.

These lesions have been divided into two groups according to roentgenologic differences based on the presence or absence of associated apical involvement.

These two groups, named the "pure" and "impure" types, show distinct differences in sex, age, history of tuberculosis contact, the mode of onset and the side affected.

Theories of localization in the lower lobe are reviewed, and evidence for confirmation of Reisner's hypothesis is presented.

A method of treatment is outlined.

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MEDICAL PROGRESS

THE PARATHYROID GLANDS AND PARATHORMONE*

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IN RECENT years a number of excellent reviews on mineral metabolism and its control by the endocrine glands have appeared. Calcium and phosphorus metabolism was comprehensively reviewed by Schmidt and Greenberg¹ in 1935, and the more recent literature in this field was analyzed by Greenberg² in 1939 and by Cohn, Cohn and Aub³ in 1942. Recent advances in the knowledge of the chemistry of calcification were reviewed by Logan⁴ in 1940, the physiology of bone and of certain bone diseases by McLean⁵ in 1943, and various aspects of phosphorus metabolism by Guest and Rapoport⁶ in 1941 and by McLean⁷ in 1942. The literature on the relation of the endocrine glands to calcium metabolism was covered by Campbell and Turner⁸ in 1942, and special aspects of this problem have also recently been reviewed, such as the physiology and treatment of parathyroid diseases (Albright⁹), secondary hyperparathyroidism (Anderson¹⁰), calcium metabolism during pregnancy (Bodansky and Duff¹¹), the use of sterols in the treatment of hypo-

parathyroidism (McLean¹²) and the influence of the endocrine glands, including the parathyroid, on growth and aging by Silberberg and Silberberg.¹³ The extensive article by Campbell and Turner⁸ is not only a complete review of the literature concerning experimental studies on the parathyroid glands but also includes the report of many original observations on numerous aspects of this subject.

EXPERIMENTAL STUDIES

Mode of Action of Parathyroid Hormone

Considerable experimental evidence has been obtained in support both of the original theory of Collip that the chief action of the parathyroid hormone is directly on the solution of calcium salts from bone and of that of Albright, who has postulated that its action consists in promoting the re-excretion of phosphate.

Supportive evidence for the renal action of parathormone was obtained by Goadby and Stace who failed to obtain the normal phosphate diuresis in patients with chronic nephritis following injection of parathyroid extract, and by Goadby,¹⁴ who was able to correlate the degree of such phosphate diuresis inversely with the degree of severity of

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renal disease. Tweedy and his associates showed that no rise of the serum calcium level occurs after parathormone injection in bilaterally nephrectomized dogs¹⁶ or rats,¹⁷ that the response is normal in a unilaterally nephrectomized dog,¹⁸ and that nephrectomy protects dogs from the characteristic pathologic changes that develop after overdosage with parathyroid hormone in normal animals.^{16, 18} Harrison and Harrison¹⁹ have developed a method for the quantitative determination of the amount of phosphate resorbed from the renal tubules, and have shown that in dogs following parathormone administration there is a decrease in the rate of maximal resorption, with reduction in the level of serum inorganic phosphorus. Induced acidosis resulted in the same reduction in tubular resorption of phosphate as parathormone.²⁰ Fay, Behrmann and Buck,²¹ on the other hand, found no difference in the renal clearance of phosphate and creatinine between normal, hyperparathyroid and parathyroidectomized dogs. Brull and Carbonesco²² concluded from the results of a cross-circulation experiment that parathyroidectomy reduces the excretion of renal phosphate owing to a purely renal effect. Neufeld and Collip²³ produced renal insufficiency in dogs, rats and cats in a variety of ways and were unable to demonstrate any change in the serum calcium level following the administration of parathyroid extract. These authors also found that in normal animals continuous administration of disodium phosphate with parathormone resulted in the maintenance of normal values of serum calcium and phosphorus. All these findings favor the theory of increased renal excretion of phosphate under the influence of parathyroid hormone.

On the other hand, Ellsworth and Fletcher²⁴ found a rise in the serum calcium level after treatment of nephrectomized dogs with parathyroid extract, and concluded that the renal elimination of phosphorus was not prerequisite to this rise. After similar treatment of chronic nephritic patients a rise in the calcium levels sometimes occurred after twenty-four hours,²⁴ and in nephrectomized rats similarly treated, although no rise of this level was observed, osteoclastic resorption of bone was demonstrated.¹⁷ Similarly, Seyle²⁵ found that in rats nephrectomy does not prevent the characteristic osteoclastic resorption of bone that follows administration of parathormone, whereas parathyroidectomy does prevent the much less striking bone changes that result from nephrectomy alone. Logan²⁶ obtained the typical rise of urinary and fall of serum phosphorus levels after injection of parathyroid extract into normal dogs, but also observed a rise in the serum calcium level within one hour whether or not the phosphorus level was simultaneously lowered. Moreover, twelve to twenty-four hours later both the calcium and phosphorus levels of the serum were elevated. Ingalls, Donald-

son and Albright²⁷ studied the effects of parathormone on nephrectomized rats and found definite decalcification of bone, due specifically to the hormone. McLean and Bloom²⁸ demonstrated bone salt in the trabeculae of spongy bone of rats and puppies under the influence of parathyroid extract, both being transported to the marrow vessels and within marrow macrophages. Moore,²⁹ however, did similar experiments in rats and found that deposition of calcium phosphate in the bone marrow was always associated with focal tissue degeneration and similar deposits in other tissues. The effect of an extremely active parathormone preparation on the rate of hydrolysis of glycerophosphate by kidney phosphatase was studied by Wood and Ross³⁰ who found that the accelerating action of the hormone was nonspecific and no greater than that of serum or egg albumin. Although these studies in no way discredit the theory of increased excretion of renal phosphate under the influence of the parathyroid hormone, they do suggest that the latter may have a direct demineralizing action on the bones as well.

Cantarow and his associates,^{31, 32} from a study of the partition of calcium and phosphorus between serum and physiologic saline solution injected into the peritoneal cavity of dogs, have concluded that the fundamental action of the parathyroid hormone is to promote the diffusion of calcium from the blood into the various tissue fluids, the source being the solution of bone salts.

Miscellaneous studies on the action of parathormone include the demonstration of a rise in phosphatase activity of serum³³ and of the long bones.^{34, 35} Roche and Filippi³⁵ believe this to be due to an increase in the concentration of enzyme activators at these sites. Cantarow, Haury and Whitbeck³⁶ found that in dogs parathormone caused a drop in the serum magnesium level, with a rise in that of the peritoneal fluid. Previously, Tibbetts and Aub³⁷ had shown that magnesium excretion is normal in hyperparathyroidism, although cure of the disease is accompanied by a temporary fall and parathormone administration by a temporary rise of this element in the urine. Increase in the magnesium intake resulted in an increase in the calcium excretion, and these authors suggest that magnesium may be substituted for calcium in the bones in this disease. Cantarow, Brundage and House³⁸ report hyperproteinemia due to hemoconcentration in experimental hyperparathyroidism in dogs. Shelling, Kajdi and Guth³⁸ found that after the injection of parathyroid extract into dogs there was a marked initial diuresis, with a resultant loss of water and electrolytes, which, if repeated, was followed by the usual syndrome of parathyroid "poisoning," with urinary suppression and death. They were able to prevent the latter condition by replacement of fluid and electrolytes, and concluded from this that de-

hydration is an important element in this experimental syndrome. Intestinal absorption of calcium is not affected by oversecretion of parathyroid hormone.³⁹ Cantarow, Stewart and Housel⁴⁰ have studied the pathologic effects of large doses of parathormone in dogs and report both calcification and extensive degenerative changes in the viscera. Bedinger, Kendrick and Keeton⁴¹ studied the toxic effects of calcium administered intravenously to dogs, and among other observations recorded that parathyroidectomy with a low initial serum calcium level affords no protection against these. Logan, Christensen and Kirklin⁴² were able to detect only a very slight rise in the urinary calcium level following injection of thyroid into thyro-parathyroidectomized dogs, and believed that this might indicate that the parathyroid glands are necessary for the rise of this level that usually follows such administration, although they also pointed out that the low initial level of serum calcium in these animals might in itself have prevented this characteristic effect of thyroid. Schiffrin⁴³ has reported the effects of parathormone on the gastric secretion of dogs; these are mainly a reduction of the volume and acidity and an increase of the enzyme concentration. The reverse effects result from thyro-parathyroidectomy and are due specifically to the lack of parathyroid hormone.

Relation between Parathyroid Hormone, Vitamin D and Dihydratichysterol

The relation between the parathyroid hormone, vitamin D and A. T. 10 (dihydratichysterol) has been extensively studied by Albright and his associates,⁴⁴⁻⁴⁶ who as a result of their comparison of the action of these agents in hypoparathyroidism and rickets have developed the theory that both vitamin D and A. T. 10 increase the absorption of calcium and that all three substances promote the excretion of phosphorus in the urine, but that vitamin D acts chiefly on calcium absorption, whereas parathyroid hormone acts exclusively on phosphorus excretion. A. T. 10 acts only feebly in its enhancement of calcium absorption but is extremely active in promoting the excretion of urinary phosphorus. Hence it is not antirachitic but is a good therapeutic agent for hypoparathyroidism.

Experimental evidence in support of this thesis has appeared. Thus, Shohl, Fan and Farber⁴⁷ reported that nontoxic doses of A. T. 10 prevented rickets in rats due to a low calcium and high phosphorus level but not that due to a high-calcium and low-phosphorus diet. They made the reasonable assumption that it was effective in the former by causing a greater excretion of phosphorus in the urine, thus rendering the diet less rachitogenic. Shohl and Farber⁴⁸ then showed that in approximately toxic amounts A. T. 10 nullifies the rachitogenic effects of a high-calcium and low-phosphorus diet, which is evidence that it does promote cal-

cium absorption in large doses and is therefore weakly antirachitic, although only one four-hundredth as active in this respect as vitamin D. Bastenie and Zylberszac⁴⁹ found that small doses of A. T. 10 resulted in inhibition of mitoses in the parathyroid glands of rats. They assumed that this effect was secondary to the high level of serum calcium induced by this drug. A similar inhibition of mitoses in the parathyroid glands of rats treated with large doses of A. T. 10 was observed by Campbell and Turner.⁸

Rose and Sundérman⁵⁰ studied 5 patients with postoperative parathyroid deficiency and found that A. T. 10 was extremely effective in controlling symptoms and maintaining a normal concentration of serum calcium. Himsworth and Maizels⁵¹ compared the efficacy of vitamin D and that of A. T. 10 in the control of a case of idiopathic hypoparathyroidism. Both were effective, but the former was somewhat more reliable and capable of giving perfect control of the serum calcium level if given in sufficiently large doses. Blum⁵² has reported excellent clinical results with the use of this agent for the control of hypoparathyroidism, and Rya and McCullagh⁵³ were similarly successful. All these authors found that A. T. 10 alleviated the symptoms of parathyroid insufficiency, promoted the excretion of calcium and phosphorus in the urine and controlled the serum concentrations of these substances. They consider that feeding large amounts of calcium by mouth increases the efficiency of the drug and thereby reduces the dosage of the latter necessary to control the disease.

McLean¹² has reviewed the clinical and experimental evidence on this subject and has concluded that vitamin D and A. T. 10 are equally effective in the control of parathyroid insufficiency, provided that the former is given in adequate amounts, the calcemic dosage being one hundred to two hundred times greater than the antirachitic. McLean¹² concluded that unsatisfactory results obtained with the use of vitamin D as a calcemic agent were due solely to inadequate dosage. A discussion of the relative merits of vitamin D and A. T. 10 in treating hypoparathyroidism was included in a presentation of such cases by Cutting, Wells and Carnes.⁵⁴ They found the two drugs about equally efficacious, but one of their patients was definitely refractory to A. T. 10. Sevringhaus and St. John⁵⁵ have recently reported on the continuation and confirmation of an earlier study⁵⁶ of patients with severe permanent hypoparathyroidism in whom the deficiency was perfectly controlled with vitamin D and calcium salts.

Factors Affecting the Activity of Parathyroid Gland

The pituitary and other endocrine glands. Some attention has been given to the possible elaboration of a parathyrotropic factor by the pituitary gland. Friedgood and McLean⁵⁷ found that guinea pig

injected with anterior-pituitary extract developed significant elevations of the serum calcium level. Although there was no change in the level of serum inorganic phosphorus, they interpreted these results as indicating the presence of a parathyrotropic factor in the anterior-pituitary preparation. A similar interpretation was placed by Ham and Haist⁵⁸ on their observation that anterior-pituitary extract produced a large number of mitoses in the parathyroid tissue of dogs. Blumenthal and Loeb⁵⁹ found that acid extracts of the anterior pituitary gland, hypophyseal implants and potassium iodide all increased the mitotic activity of the thyroid gland and parathyroid glands of guinea pigs, whereas underfeeding and thyroid produced the reverse effect. On the other hand, Carnes, Osebold and Stoerk⁶⁰ observed no evidence of impairment of parathyroid function in hypophysectomized rats. The serum calcium and phosphorus concentrations remained normal even under the stress of a low-calcium diet, and hypophysectomized and parathyroidectomized rats behaved in every way like those with parathyroidectomy alone. Similarly, Snyder and Tweedy⁶¹ were unable to detect any alteration in the serum calcium level and actually found a slight rise in the phosphorus level following treatment of rats with anterior-pituitary extract. In hypophysectomized monkeys Blander⁶² found a slight atrophy of the parathyroid glands as measured by size and cell count but no change in the histologic or cytologic characteristics of the cells. Campbell and Turner⁸ made extensive studies of the effect of anterior-pituitary extract on the weights and mitotic activities of the parathyroid glands of several species and concluded that the existence of a parathyrotropic factor is highly doubtful. In toads, Schrire⁶³ found no difference in the effect of injected parathyroid extract on the level of plasma inorganic phosphate between normal and hypophysectomized animals. Thus, evidence for a relation between the parathyroid glands and the anterior pituitary gland is neither consistent nor conclusive. If such a relation exists, it is probably not an extremely close one, for the former appear to be able to function even when the anterior pituitary is removed.

In rats, Bastenie and Zylberszac⁶⁴ found that folliculin inhibited and progesterone and castration stimulated the mitotic activity of the parathyroid glands. The folliculin effect was inhibited by progesterone, and the castration effect by folliculin. Treatment with both hormones greatly stimulated mitoses in the parathyroid glands of castrated but not in those of normal rats. Campbell and Turner,⁸ on the other hand, observed no change in the mitoses of the parathyroid glands of chicks treated with estradiol benzoate. Nathanson, Brues and Rawson⁶⁵ have shown that testosterone stimulates mitoses in the parathyroid glands of rats. Similar effects on the thyroid glands of these animals were ob-

served, and since testosterone in moderate doses is known to stimulate ovarian activity through the intermediation of the pituitary gland, these authors suggested that the observed effect on the parathyroid and thyroid was also via the hypophysis. Campbell and Turner⁸ were unable to confirm these findings. Bloom, McLean and Bloom⁶⁶ found that parathyroid extract abolished the proliferative endosteal reaction in medullary bone, which is a characteristic phenomenon preparative to new-bone formation following the combined administration of estrogens and androgens in pigeons.

Pregnancy. Bodansky and Duff¹¹ have stated that somewhat low serum calcium values are to be expected in pregnancy and are not to be regarded as abnormal if not below 8.5 mg. per 100 cc. Severe hypocalcemia means either parathyroid deficiency or nutritional inadequacy and results in skeletal abnormalities in the fetus. These authors regard a slightly high fetal serum calcium level as normal. In studies on rats, they found some demineralization of bones in the presence of normal serum calcium levels, presumably owing to stimulation of the parathyroid glands by a lowered serum calcium level. In parathyroidectomized animals, on the other hand, in which the skeleton showed no changes in density, lowered serum calcium levels did develop, and tetany occurred near term. It was found that pregnancy converted latent into active hypoparathyroidism in these animals, and that this condition could be cured by a high-calcium and low-phosphorus diet. Bodansky⁶⁷ studied the mineral metabolism of pregnant women and observed evidence of increase in the size and functional activity of the parathyroid glands such that he characterized pregnancy as a state accompanied by a minor degree of hyperparathyroidism. He found a rise of serum phosphatase activity in the last trimester, accompanied, however, by a slight degree of hypocalcemia and little change in serum inorganic phosphorus. In a similar vein, Sinclair⁶⁸ showed that pregnancy resulted in marked hypertrophy of the parathyroid glands of rats and that multiparity had a cumulative action in this respect. The hypertrophy could be prevented by a high-calcium and low-phosphorus diet but was enhanced by a diet low in calcium and rich in phosphorus. Similar effects of pregnancy on the volume of the parathyroid glands of rats were reported by Oppen and Thale.⁶⁹

In studying the relation of parathyroid activity to pregnancy in rats, Bodansky and Duff⁷⁰ found that parathyroidectomy resulted in diminished fertility and reduction in the number and birth weight of the fetuses. These effects were minimized by feeding a high-calcium and low-phosphorus diet. In addition, the parathyroidectomized animals underwent a prolongation of gestation, showed tetany at term and suffered a high rate of maternal

and fetal mortality. These effects were abolished by a high-calcium and low-phosphorus diet. In another study,⁷¹ pregnant parathyroidectomized rats were again shown to be unable to mobilize calcium from their bones, so that the latter retained their normal pregestational weight and hypocalcemia developed. With a rachitogenic diet with a high calcium-to-phosphorus ratio, the differences in bone weights between the pregnant parathyroidectomized and normal control rats were abolished.

Cantarow, Stewart and Housel⁴⁰ noted that in the case of a pregnant dog treated with toxic amounts of parathyroid extract and from which nine normal living fetuses were obtained, none of the characteristic pathologic changes observed in the mother were found in the fetuses, suggesting that the parathyroid hormone cannot pass the placental barrier. Bodansky and Duff,⁷² from studies on fetal growth and storage of calcium and phosphorus with varying conditions of diet and parathyroid function in pregnant rats, concluded that fetal growth and mineral storage depend entirely on suitable concentrations of calcium and phosphorus in the maternal blood, which it was assumed are accurately reflected in the fetal blood as well. Sinclair⁷³ found that the parathyroid glands of fetal rats were twice as large in proportion to the body weight as those of adults and were affected by the diet of the mother as a result of changes in her serum calcium or phosphorus level. A diet with a normal ratio of calcium to phosphorus caused enlargement of maternal parathyroid glands, and one with more calcium and less phosphorus tended to suppress changes in both maternal and fetal glands. Such a diet, however, was effective therapeutically after maternal parathyroidectomy. A normal diet to which aluminum acetate was added to reduce phosphate absorption was equally effective under these circumstances. The parathyroid glands of fetal rats were depressed by a high serum calcium or inorganic phosphorus level in the mother. Sinclair found the total weight of the tissue of all the parathyroid glands in fetal animals to be only 5 per cent of that of adults, so that it is probable that pregnancy can afford little protection against the consequences of parathyroidectomy in the mother. It appears clear from these as well as previous studies that pregnancy exerts a great strain on the parathyroid calcium system of the mother, and that this is a period of human life when most careful attention should be given to the calcium and phosphorus content of the diet.

Diet and serum calcium level. Baumann and Sprinson⁷⁴ have produced experimental hyperparathyroidism in rabbits by feeding a high-phosphorus and low-calcium diet. The parathyroid glands enlarged with hypertrophy of the cells, and an increase in the amount of circulating parathyroid hormone was suggested by results obtained with

the technic of Hamilton and Schwartz. Ham, Littner, Drake, Robertson and Tisdall⁷⁵ concluded from their experiments that parathyroid hypertrophy occurs only in low-calcium, not in low-phosphorus, rickets and that it is a function only of the serum calcium level. They interpreted their results as indicating that hypocalcemia, not hyperphosphatemia, is the factor that stimulates parathyroid activity. DeRobertis,⁷⁶ on the other hand, has reported that parathyroid hypertrophy, with enlargement and hyperplasia of the cells whose cytologic characteristics become suggestive of marked functional activity, occurs both in rats with low-calcium and in those with low-phosphorus rickets, although the effect is more striking in the former. Similar studies on rats by Carnes, Pappenheimer and Stoerk⁷⁷ also revealed that an increase in parathyroid volume occurs on a low-calcium and a decrease on a low-phosphorus diet. When the calcium of the diet was maintained at a constant value, the parathyroid volume was approximately proportional to the amount of dietary phosphorus. The giving of viosterol led to a rise of both serum calcium and phosphorus with a low-phosphorus diet and enhanced the diminution in size of the parathyroid glands. This agent, however, caused an inhibition of the parathyroid enlargement obtained with a low-calcium diet.

Patt and his associates^{78, 79} studied the effects of oxalate and of perfusion of the parathyroid glands with decalcified and normal blood on the serum calcium of normal and parathyroidectomized dogs. They concluded that a lowering of the serum calcium level directly stimulates the glands to produce more hormone. Selye²⁵ noted that parathyroid extract exhibited its usual action in rats previously subjected to partial thyroidectomy or partial hepatectomy, and concluded that the activity of this hormone is not affected by either the liver or the thyroid gland.

An interesting corollary to the effect of diet on the functional activity of the parathyroid glands is the effect of the latter on the mineral appetite of experimental animals. The work of Richter and his associates has shown that the appetite of rats for calcium lactate⁸⁰ and other calcium salt solutions⁸¹ is markedly increased by parathyroidectomy, this change being reversed by parathyroid implants,⁸⁰ the injection of large amounts of parathormone or the addition to the diet of various materials rich in vitamin D or of A.T. 10.⁸² An increase in the appetite for strontium and magnesium salts and an aversion to disodium phosphate solution were also observed following parathyroidectomy.⁸¹ Richter and Birmingham⁸² have utilized this appetite method for the bioassay of various substances having an effect on the metabolism of calcium. Wilens and Waller,⁸³ using the method of Richter,⁸⁰ showed that partially nephrectomized rats voluntarily consume increased

counts of water and the same amount of calcium preoperatively but decreased amounts of phosphorus. Parathyroidectomized rats increase their calcium and decrease their phosphorus intake, and such animals subjected to partial nephrectomy will consume an even greater amount of calcium and small amounts of phosphorus.

The kidneys and renal function. The fact that reactivity of the parathyroid glands can produce renal damage has always been of interest, and here is a nephritis produced by one's own secretions. Renal insufficiency may also produce an enlargement of the parathyroid glands, and additional work on this subject has recently been reported. The investigations of Donohue, Spingarn and Pappenheimer⁸⁴ showed that partially nephrectomized rats exhibited an increase in the calcium of the remaining renal substance. This was apparently associated with an observed coincident parathyroid enlargement, for it could be prevented by parathyroidectomy. Duguid⁸⁵ found that in rats with chronic nephritis due to a high-phosphate, high-vitamin D diet, parathyroid hypertrophy occurred, but since it was found also in animals on such a diet that did not develop renal changes, he concluded that it was the result of a disturbance of phosphorus metabolism and that the relation of nephritis was still uncertain. Chown and his co-workers^{86, 87} have studied the renal pathologic changes that develop after administration of parathyroid extract to rats, and believe that they result from calcium deposition both inside and outside of the nephrons, causing obstruction with either atrophic changes or tubular dilatation. The gross lesions observed fell into three categories: cystic dilatation of the tubules, irregular dilatation of the pelvis and chronic focal nephritis. The authors suggest that disturbances in mineral metabolism may be the background for some clinical cases of polycystic kidneys and pyelonephritis.

The Parathyroid Glands and Growth, Repair of Fractures and So Forth

In an extensive study of the effects of parathyroid extracts on the skeletons of growing rats, Burrows⁸⁸ found that the hormone caused a retardation of growth and hypoplasia of the parathyroid tissue. On the skeleton the early effects consisted of the classic type of demineralization and the production of characteristic osteitis fibrosa. If administration of the extract was continued, a reversal of this phenomenon was observed, and marked osteoblastic activity brought about a state akin to marble bone disease. Later this effect also tended to diminish, and the bones to return to an essentially normal state. The author has discussed the possible significance of these findings.

Roche and Mourgues⁸⁹ have reported that in pigeons with experimental fractures treated with vitamin D₂ or parathyroid hormone, although there

was no acceleration of callus formation, there was a significant increase in the bone salt content of the calluses of the treated pigeons over that of the calluses of the untreated controls. In the parathyroid-treated birds mild generalized skeletal demineralization occurred. These authors discuss the therapeutic implications of these findings in the treatment of fractures. Silberberg and Silberberg⁹⁰ have recently shown that in mice parathyroid hormone causes hypertrophy, calcification and breakdown of growing epiphyseal cartilage plates. The hormone results in osteoblastic but not in cartilaginous proliferation. Since there was acceleration of epiphyseal closure, the authors concluded that the hormone speeds up the characteristic changes observed in the normal aging process of the skeleton. In old mice with united epiphyses, calcification of inactive cartilage and increased bone formation occurred after parathormone treatment. Similar effects were obtained with the use of calcium gluconate, but combination of the latter with parathormone, although producing a marked increase in bone formation, had no effect on the changes typical of skeletal aging. These observations are interesting, but it must be borne in mind that the reactions of the bones in rats and birds are not the same as those observed in dogs and men.

The Nature of Parathyroid Hormone

Ross and Wood⁹¹ have developed a method for preparing a parathyroid extract that apparently consists of relatively pure parathyroid hormone and that has triple the potency of all previous extracts. Ultracentrifugation showed the presence of two gross molecular species, the molecular weight of one being in the neighborhood of 20,000 and that of the other between 500,000 and 1,000,000. After complete sedimentation of the latter, 50 per cent of the hormonal activity was retained in the mother liquor, suggesting that the smaller molecule is the parathyroid hormone. Pepsin digestion of the whole extract destroyed its activity, ultraviolet absorption studies revealed no chromophoric prosthetic group, and the preparation was stable to electrodialysis, showing that the hormone has no loosely bound polar groups of low molecular weight. These studies therefore confirm the previously suspected protein nature of the parathyroid hormone, which is further strengthened by the studies of Wood and Ross⁹² on the ketene acetylation of the hormone, the result of which is complete inactivation, not reversed by subsequent hydrolysis. From this the authors conclude that free amino groups are necessary for the physiologic activity of the hormone.

CLINICAL ASPECTS

Hypoparathyroidism

Drake, Albright, Bauer and Castleman⁹³ have discussed the criteria necessary for making the

diagnosis of chronic idiopathic hypoparathyroidism and consider that the following clinical findings are necessary prerequisites: a low serum calcium level, a high serum inorganic phosphorus level, a normal skeleton by roentgenography and absence of all signs of renal insufficiency. These authors review all the available proved cases of the disease and discuss possible etiologic factors. The pathologic findings in 1 of the 2 proved cases in which these are available are cited, and include complete replacement of all the epithelial cells of the parathyroid glands by fat. In the case with post-mortem findings reported by Cantarow, Stewart and Morgan,⁹⁴ no parathyroid tissue was identified.

McQuarrie, Hansen and Zeigler⁹⁵ studied factors affecting tetany production in a case of idiopathic hypoparathyroidism apart from the level of serum calcium. They found that a low-mineral diet increased the convulsive tendency as provoked by various kinds of stimuli, whereas a high-mineral diet had the opposite effect even without changes in the levels of serum calcium and phosphorus. Hyperventilation induced tetany during feeding of a low-mineral but not of a high-mineral diet. Tetany produced by the antidiuretic effect of posterior-pituitary extract was lessened by addition of salt, which presumably cut down the dilution of the extracellular fluid due to water retention. The authors concluded that in hypoparathyroidism the convulsive tendency is due to more than a low serum calcium level. This is in line with the findings of Evans, Szurek and Kern⁹⁶ in surviving parathyroidectomized dogs. These investigators found that such animals remained in latent survival with low serum calcium and high serum phosphorus levels without showing signs of tetany, and concluded that some adjustment in neuromuscular irritability must occur so that it becomes normal in spite of an abnormal electrolyte pattern in the tissue fluids.

Robertson⁹⁷ has reported studies on calcium and phosphorus metabolism in cases of postoperative tetany. He found the usual fall in the urinary phosphorus level and elevation of the serum phosphorus level with a drop in both serum and urinary calcium levels, but noted that a fall of the urinary phosphorus level might also occur in uncomplicated thyroidectomy. He also observed in a patient with a serum calcium level of 5.5 mg. per 100 cc. that a normal ratio of fecal to urinary calcium excretion was maintained. This appeared to him to render unlikely the theory that a serum calcium level of about 8.5 mg. per 100 cc. is the renal threshold level for its excretion.

Albright, Burnett, Parson and Sulkowitch⁹⁸ state that in the case of a patient with hypoparathyroidism whom they studied the ingestion of aluminum hydroxide caused a lowering of the serum phosphorus level and an elevation of the serum calcium level, the effect presumably being due to de-

creased phosphorus absorption as a result of the formation of insoluble aluminum phosphate compounds in the bowel.

Several examples of the not uncommon trophic disturbances in tissue of ectodermal origin, including skin lesions, loss of nails and hair and cataract formation, in association with hypoparathyroidism have been reported.^{99, 100} Albright, Burnett, Smith and Parson¹⁰¹ have called attention to a syndrome that they term "pseudohypoparathyroidism" in which the classic clinical and laboratory manifestations of parathyroid insufficiency are present, but in which the essential disturbance is apparently not a lack of parathyroid hormone but rather a failure of end-organs to respond normally to it, since the changes are not reversed by its administration and phosphate diuresis similarly fails to occur. In 1 of 3 such patients studied, normal parathyroid tissue was observed at biopsy. Recently Sutphen, Albright and McCune¹⁰² have reported on the remarkable occurrence of hypoparathyroidism in 3 siblings; in 2 of these cases the disease was associated with widespread moniliasis, and presumably also in the third. Two other cases of association of these diseases were cited, together with 2 cases of associated moniliasis and Addison's disease, in 1 of which there was also hypoparathyroidism. The times of onset of symptoms in these cases suggested that the moniliasis preceded the parathyroid insufficiency. The authors have discussed the possible etiologic significance and relations of these unusual observations.

Hyperparathyroidism

An enlightening résumé of the historical development of knowledge concerning this disease may be found in a recent article by Cope,¹⁰³ which also includes an excellent discussion of the two types of pathologic changes that may result in clinical hyperparathyroidism, either adenoma or hyperplasia of the glands. Soffer and Cohn¹⁰⁴ have prepared a review of the literature on primary and secondary hyperparathyroidism, together with a presentation of 5 primary and 4 secondary examples of this disease. One of their cases is of special interest in that the patient apparently had a primary adenoma with hyperparathyroidism that resulted in renal damage and chronic renal disease, the latter, in turn, leading to secondary hyperplasia of the other parathyroid glands. A similar case was studied by Downs and Scott,¹⁰⁵ who were able to reconstruct such a clinical course on the basis of autopsy findings. Snapper¹⁰⁶ has presented an analysis of 3 cases of parathyroid adenoma, 1 of which was of interest because of the finding of a low urinary calcium in combination with the usual biochemical changes associated with hyperparathyroidism. This was attributed to a probable superimposed vitamin D deficiency. Lage and Greene¹⁰⁷ have reported 13 cases of hyper-

parathyroidism from the Middle Western states, an area in which this disease is considered a great rarity. Ansbach and Clifton¹⁰⁸ studied 2 cases of parathyroid adenoma in children. In 1 case the onset of the disorder was at three months of age, the youngest such patient known. Another unique feature reported was relief of symptoms and good recalcification of the skeleton following x-radiation of the neck. Jacox, King and Bailey^{109, 110} studied a patient with clinical hyperparathyroidism and advanced bone lesions in whom no parathyroid tumor or hyperplasia could be demonstrated surgically and in whom some recalcification of the skeleton, improvement in blood chemical findings and symptomatic relief followed x-radiation of the neck. The patient subsequently died of renal failure, apparently secondary to calculus formation and obstruction of the urinary tract. At autopsy no parathyroid tissue was identified, presumably because of the radiation therapy. It is difficult to account for the fact that the patient terminally still exhibited the blood findings characteristic of hyperparathyroidism. Cope^{111, 112} has discussed the surgical management of hyperparathyroidism and laid stress on the specialized knowledge, training and technics involved. An analysis of the distribution of parathyroid tissue, together with observations concerning recognition of its normal and abnormal states and details concerning the surgical removal of diseased glands, are included, as well as a description of the two-stage exploratory procedure used in such cases at the Massachusetts General Hospital. In these operations an initial exploration of the neck and posterior mediastinum is made, and if no parathyroid adenoma or hyperplasia is discovered, search for a tumor in the anterior mediastinum is made at a second session. Three cases of parathyroid adenoma, 2 with unusually located tumors, were reported by Cochran,¹¹³ whose results led him to suggest the possible efficacy of partial as against complete removal of such lesions. Meyer and Ragins¹¹⁴ have reported the clinical and pathological findings in a remarkable case of proved parathyroid carcinoma with hyperparathyroidism, fibrocystic disease and renal lithiasis, all three of which conditions improved after excision of the original tumor but reappeared with recurrence of the lesion and the development of metastases. This is an extremely rare condition.

Hansman and Carr Fraser¹¹⁵ found that in patients with hyperthyroidism generally, but not invariably, there was an associated negative calcium-and-phosphorus balance that could not be correlated with the change in metabolic rate and was unaffected by Lugol's solution. The balance was, however, rendered normal by radiation therapy. These findings led them to conclude that hyperfunction of the thyroid gland and that of the parathyroid glands are often associated, and that by plastic parathyroid cells are radiosensitive.

view of such cases has been presented in connection with the report of a case by Miller and Evans¹¹⁶ of simultaneous thyroid hyperplasia and parathyroid adenoma proved pathologically. A topic of interest in connection with hyperparathyroidism is the finding by Klendshoj and Koepf¹¹⁷ of a high acid as well as a high alkaline phosphatase level in the serum of a patient proved to have this disease. This is the only reported example of another disease in which the acid phosphatase level was elevated to the same extent as occurs in carcinoma of the prostate with skeletal metastases. The fact that the presenting symptoms of hyperparathyroidism may be the result of changes in the oral cavity has been brought out by Strock¹¹⁸ in a discussion of the dental symptoms that may be associated with this disorder.

The subject of secondary hyperparathyroidism has been well reviewed by Anderson.¹⁰ Herbert, Miller and Richardson¹¹⁹ have studied a case of chronic renal disease with secondary parathyroid hyperplasia, decalcification of bone and metastatic calcification and have reviewed similar cases. They have attempted to set a standard for the saturation level of serum calcium and phosphorus above which metastatic calcification may be expected to occur. This they anticipate only in cases such as the one presented in which the combination of renal disease and secondary hyperparathyroidism produced an elevated serum phosphorus level together with a normal or high serum calcium level. Ginzler and Jaffe,¹²⁰ however, have concluded that the osseous lesions of chronic renal disease are usually the result of acidosis rather than of hyperfunction of the parathyroid glands, which in most cases were only mildly hyperplastic. The problem of secondary hyperparathyroidism produced by obstructive lesions of the urinary tract in children has been discussed by Harrison,¹²¹ who reports clinical observations and the results of treatment of 5 such patients.

Albright, Burnett, Cope and Parson¹²² have published an excellent short discussion of their views concerning the active metabolism of bone and the fundamental physiologic disturbances underlying the development of osteitis fibrosa, osteoporosis and osteomalacia. They point out that although the serum calcium, phosphorus and phosphatase values are normal in osteoporosis, since there is hypercalciuria, renal damage may ensue, and hypercalcemia may develop, especially if the rate of calcium excretion is insufficient to keep up with that of demineralization of the bones. Under these circumstances a mistaken diagnosis of hyperparathyroidism is likely to be made, and these authors have presented a case illustrating this possibility.

From the foregoing discussion it should be clear that in the last few years considerable progress has been made in the understanding of both the normal and the pathologic physiology of the parathyroid glands.

glands. Experimental studies have indicated that the parathyroid hormone probably acts both to promote the renal excretion of inorganic phosphorus and to bring about directly the solution of bone salts. Clinical and physiologic investigations have greatly clarified the modes of action and relations of parathyroid hormone, vitamin D and A.T.10. The treatment of hypoparathyroidism has been rendered simple and effective, and the surgical management of hyperparathyroidism placed on a sound basis.

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Correction. In the report on medical progress, "Hematology," by Dr. William Dameshek, which appeared in the April 27 issue of the *Journal*, the word "donor's," which appears in lines 4 and 7 of the second column, on page 517, should be replaced by the word "recipient's"

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

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EDITH E. PARRIS, *Assistant Editor*

CASE 30231

PRESENTATION OF CASE

First admission. A thirty-four-year-old woman was admitted to the hospital because of jaundice and fatigue.

About one year before admission, the patient was sent to the Out Patient Department because of two positive Hinton tests. There was no history of primary or secondary syphilis. Repeat Wassermann and Hinton tests were positive. X-ray studies of the chest and cerebrospinal fluid examinations were negative. Physical examination was also entirely negative. Treatment with bismuth and subcarbonate was started, and she received twelve doses of 0.2 gm. each, followed by eight injections of Mapharsen of 0.03-0.04 gm. each. After each injection of Mapharsen she had nausea and vomiting for one or two days and felt weak. She was given another course of bismuth subcarbonate (0.2 gm.) and seven intravenous injections of neoarsphenamine (0.45 gm.). Her general weakness, tiredness, headache, various joint aches and occasional nausea and vomiting continued and became constant, and she was forced to give up her job. She had no appetite and lost about 28 pounds in weight. In the last few weeks of the treatment she began to notice a steadily increasing yellowish pigmentation of the skin. All her symptoms seemed to become aggravated and she was admitted to the hospital.

Examination showed a thin, alert woman. The skin was dry and "jaundiced," the color being described as yellowish brown on the face, dorsum of hands and knees and brown on the palmar creases. There was a "bismuth line" around the teeth. Small patches of ecchymoses and hemorrhagic spots were seen on the back and on the inner surfaces of the lower extremities. There was yellowish pigmentation of the scleras and conjunctivas. Generalized enlargement of the cervical, axillary and epitrochlear lymph nodes was noted, but examination was otherwise essentially normal.

The blood pressure was 100 systolic, 70 diastolic. The temperature was 98°F., the pulse 90, and the respirations 20.

*On leave of absence.

Examination of the blood showed a red-cell count of 4,650,000, with a hemoglobin of 14.2 gm. The white-cell count was 9900, with 66 per cent neutrophils. The urine was acid and had a specific gravity of 1.030. A foam test was positive for bile; there was a + test for acetone and a rare hyaline cast. The stools were light yellow to brown and occasionally guaiac positive. The blood protein was 5.9 gm. per 100 cc. The prothrombin time was 20 seconds (normal, 20 seconds), and the hematocrit 51. The van den Bergh was 6.4 mg. per 100 cc. direct, and 9.3 mg. indirect. The blood chloride was 83.6 milliequiv. per liter. Repeat chloride determinations were 96.7 and 91.4 milliequiv. per liter. The sodium was 128.2 milliequiv. per liter; the blood sugar was 82 mg. per 100 cc. The carbon dioxide combining power was 21.8 millimols per liter. A glucose tolerance test revealed a fasting blood sugar of 36 mg. per 100 cc., 162 mg. at the end of one hour, 85 mg. at the end of two hours, and 64, 59 and 43 mg. at subsequent successive half-hour periods. A cephalin flocculation test was + in twenty-four and forty-eight hours.

The patient continued to vomit and was given daily infusions of glucose and saline solutions and several transfusions. The electrolyte levels were sustained by this method, but she continued to take and retain little by mouth. The vomitus varied in amount, was guaiac negative and contained free hydrochloric acid. A mousy odor was noted in the breath. A blue-gray streaking of the hard palate and the undersurface of the tongue and patches on the buccal mucosa were seen at the end of the first week. A plain film of the abdomen showed no areas of calcification. A 17-ketosteroid determination showed that 2.8 mg. was excreted in twenty-four hours. After the first week she received daily doses of sodium acid phosphate, Hykinone and sodium chloride. The vomiting stopped, and she was able to take and retain a high-calorie, high-vitamin diet. Although still jaundiced, the van den Bergh dropped to 1.2 mg. direct and 1.8 mg. indirect and the cephalin flocculation time became zero; the blood sodium remained at about 128 milliequiv. per liter. The patient was finally discharged two months after admission.

Second admission (three months later). Following discharge the patient did well, had no nausea or vomiting and gained about 3 pounds. She had considerable craving for salt, but whether this was real or merely because she had been advised to use more salt could not be ascertained. The pigmentation disappeared from the scleras but was persistent in the skin. For the first time in her life, however, she was bothered by the cold and her hands and feet blanched on exposure to cold. About two months after discharge she had a mild upper respiratory infection, felt extremely tired and depressed and had no appetite. She recovered from this episode, however, and for the next three weeks

felt fairly well. About a week before readmission, she contracted another cold. In the next few days she became gradually weaker and more tired. Two days before admission she commenced to vomit after eating or drinking. This progressed and became almost constant. One hour before entry she developed a dull, steady, slight pain in the epigastrium, which extended under the sternum.

Physical examination showed an emaciated woman who was vomiting and in marked distress. The skin was dark tan, especially over the exposed parts. Some dark-gray pigmentation and stippling of the hard palate were noted. There were tachycardia and gallop rhythm at the apex. Examination was otherwise the same as on the first admission.

The blood pressure was 80 systolic, 70 diastolic. The temperature was 98.6°F., the pulse 110, and the respirations 20.

Examination of the blood showed a red-cell count of 4,400,000, with 12 gm. of hemoglobin. The white-cell count was 9200, with 55 per cent. neutrophils. The urine had a specific gravity of 1.018 and a pH of 5.0 and gave a +++ test for acetone; there were occasional hyaline casts. One stool was brown and guaiac positive. The blood chloride was 97 milliequiv. per liter, the sodium 125.2 milliequiv. The carbon dioxide combining power was 19.0 millimols per liter. The nonprotein nitrogen was 18 mg. per 100 cc., and the protein 6 gm. The van den Bergh was normal.

The patient was given 10 cc. of adrenocortical extract intramuscularly, followed by 20 cc. in 3000 cc. of 10 per cent dextrose in normal saline. In the next two or three days the blood chloride became 107.4 milliequiv. and the sodium 135.9 milliequiv. per liter. A diuresis test showed the volume of the night specimen to be larger than that of the morning specimen. On the fifth day the blood chloride was 101.7 milliequiv. per liter. The blood urea nitrogen was 5.6 mg. per 100 cc. The urine chloride was 116 milliequiv. per liter, and the urine urea 172 mg. per 100 cc. The daytime volume of urine was 130 cc., and the night volume 200 cc. She had three intramuscular injections of eschatin (adrenocortical extract) on the fourth, fifth and sixth hospital days, following which she improved considerably and the vomiting ceased. The stool was guaiac negative. A 17-ketosteroid assay showed an excretion of 2.8 mg. in twenty-four hours. The cephalin flocculation time was normal. The prothrombin time was 20 seconds (normal, 22 seconds). The hematocrit was 34.7. A spinal tap was normal. She was discharged on the seventeenth hospital day on an added salt intake (5 gm. daily).

Final admission (six days later). Following discharge she remained well for three days. She had no nausea, vomiting, fatigue or lethargy. On the fourth day she complained of tightness across the chest, which persisted. She had no pain, cough or weakness. The following night she could not

sleep because of a "feeling of impending disaster." Thirteen hours before entry the temperature was 101°F. She was listless and began to vomit. Throughout the day she became progressively weaker and extremely "tired." The temperature dropped to normal. One hour before admission the extremities turned blue, she was cold and clammy, the pulse could not be obtained, and she became stuporous.

Examination showed a cyanotic moribund patient with a spastic right arm held in flexion. She was frothing at the mouth, and the jaws were tightly clenched. She moved all extremities when stimulated. Respirations were shallow. The heart sounds could not be heard, and the pulse and blood pressure could not be obtained. Immediately after admission 25 cc. of Wilson's adrenocortical extract was given intravenously, along with 10 per cent of dextrose in saline. In fifteen minutes she became active. She was given oxygen and another 10 cc. of the extract intravenously, followed by a similar dose intramuscularly. She received about 1250 cc. of the dextrose solution in the course of two hours. At the end of that period she suddenly choked, frothed slightly at the mouth, gave a few gasps and stopped breathing.

DIFFERENTIAL DIAGNOSIS

DR. GEORGE W. THORN*: A thirty-three-year-old woman was first seen because of two positive Hinton tests, which were subsequently checked. Antisyphilitic treatment — two courses of bismuth, one of Mapharsen and one of neoarsphenamine — was then instituted. At the end of a year she became jaundiced, was admitted to the hospital, stayed two months, went home for three months, came back for a relatively short period, went out again, returned and died. The questions are: Was syphilis the sole cause of her trouble? Were heavy metals the sole cause of her trouble? Did heavy metal intoxication complicate syphilitic infection? Was there some complication totally independent of heavy-metal therapy and syphilis?

The first point to take up is the jaundice. Jaundice as we know, occurs in approximately 1 to 2 per cent of patients with syphilis who are treated with arsenicals. It is about seven times as frequent in patients who are treated with arsenicals for syphilis as it is in patients with syphilis who do not receive arsenical treatment. In other words, there is seven times the chance of having jaundice due to heavy-metal therapy as compared with the possibility of jaundice on the basis of syphilis alone.

The jaundice reactions that occur in syphilitic patients with heavy-metal intoxication are interesting and can be placed in three groups. The first is the jaundice that immediately follows the *first* injection of neoarsphenamine, associated with a Jarisch-Herxheimer reaction. This type of jaun-

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dice is usually not serious; it is transient and is supposedly due to the killing of large numbers of spirochetes. Another type of jaundice is that associated with "ninth-day erythema." In this reaction jaundice with chills and fever develops ten to twelve hours after the second or third injection of neoarsphenamine and it is quite readily diagnosed. It is not due to a hepatitis. In the majority of patients the jaundice disappears. This type has all the appearances and all the laboratory findings characteristic of obstructive jaundice. The phosphatase is over 10 Bodansky units, and the cholesterol over 250 mg.; the cephalin flocculation is low or negative. Hanger and Gutman¹ are responsible for describing this particular type of jaundice due to neoarsphenamine. It is different from the third type of jaundice or ordinary hepatitis, which one sees at any time during the course of neoarsphenamine, and which may occur as long as two, three or even four months following the cessation of heavy-metal therapy.

One other point before we embark on the chemical studies is the significance of the positive Hinton tests. We all know that false positives occasionally occur. One of the most illuminating pieces of information that has come out of the Army recently is that a primary take following smallpox vaccination is probably associated with one of the highest incidences of falsely positive Wassermann or Hinton reactions. From 10 to 20 per cent of persons develop a positive reaction after vaccination. One to two months later, however, the titer falls off and the reaction becomes negative. This is true of other infections that are associated with falsely positive serologic tests.

The important thing to me in a patient who has no physical evidence of syphilis and no history of primary or secondary disease is to be sure that the positive test represents syphilis. I think we can assume that it does in this case, because positive tests were recorded over some period of time. In the absence of a primary or secondary lesion, the Army and Navy follow a person with positive tests for a month or two before assuming that they are due to syphilis.

How much of this patient's illness may we attribute to heavy-metal therapy? What type of jaundice did she have? The ninth-day erythema, or the more frequent hepatitis? It is difficult to say. Certainly she did not give the characteristic picture of ninth-day erythema. Nausea and vomiting associated with jaundice suggest that she had some reaction in the liver to heavy-metal therapy. That is my first thought, and we have no evidence, as we go along, of any other disturbance that would cause jaundice except for the courses of bismuth. It is rather interesting that some patients treated with bismuth alone develop jaundice. In most cases, however, this occurs after ten or twelve injections, and may appear one or two weeks after the dis-

continuance of therapy. I suspect that this woman had a relatively mild degree of parenchymal involvement of the liver. One wonders whether the reaction was delayed, whether the patient was sensitive to the drug, or whether she had some underlying disease that gave her poor resistance to the injections. It is interesting that no jaundice developed until a second course of neoarsphenamine was given. We know that neoarsphenamine causes jaundice much more frequently than does Mapharsen, and logically, the addition of neoarsphenamine to the treatment may have been responsible for the jaundice.

Considerable interest centers around the serum chloride level of 83.6 milliequiv. per liter. What can produce that? Are low electrolytes caused by adrenal insufficiency? That is our problem. Did she have adrenal insufficiency before she was given treatment or did the toxicity of a heavy metal cause it? Of the patients with syphilis and Addison's disease, relatively few prove to have syphilis of the adrenal glands, although it is referred to in every textbook and article that I know of. Most reports discuss patients with symptoms of Addison's disease who, when given arsenical treatment, become asymptomatic, and it is concluded, without pathological data, that the patient had syphilis of the adrenal glands. In my experience, patients with Addison's disease do not tolerate antisyphilitic treatment, and I am quite convinced that this patient did not have Addison's disease at the time she was given the last injection of neoarsphenamine. I should expect such therapy to have induced collapse if she really had severe adrenal insufficiency.

If Addison's disease is not the cause of the disorder of sodium and chloride, what could have induced these changes? Low sodium and chloride can occur in patients who are vomiting and in patients who have a high concentration of organic acids in the blood, which is consistent with liver disease. The glucose tolerance test was normal, unlike that in patients with Addison's disease, when glucose absorption is disturbed.

The pigmentation is striking, but pigmentation is also typical of bismuth poisoning and helps us little in this difficult diagnosis.

She was given a vitamin K preparation. I do not know why the sodium acid phosphate was given. The jaundice improved, and she was discharged. For three months she had considerable craving for salt, and then was readmitted. She had had two colds or two upper respiratory infections, but she came back with a temperature of 98.6°F.—a patient with Addison's disease in moderate collapse has hypothermia. The pulse rate was 110. The patient was extremely weak and tired, which suggests possible myocardial change. The blood pressure was low. An interesting point is that while she was at home the blood chloride was 97 milliequiv., and the sodium 125 milliequiv. One

never sees this discrepancy in Addison's disease, and that is suggestive, if the chemical values are true, of a type of renal disease in which the chloride is retained in excess of sodium. If you give sodium chloride to a patient of this type you raise the sodium and chloride milliequivalent for milliequivalent. You will notice later that the chloride came up to 107 milliequiv. and the sodium to 135 milliequiv. I should say that a patient with Addison's disease associated with heavy-metal poisoning would not do well at home on salt, without hormone therapy.

There are two other features of great interest. She had free hydrochloric acid in the stomach. One rarely sees that in a patient with Addison's disease. The second point is that on the second admission there was a +++ test for acetone in the urine, which is rarely if ever seen in Addison's disease or in a severe liver disturbance. At that time, the van den Bergh was normal, the jaundice had disappeared, and she was given adrenocortical extract and intravenous glucose solution. Since 3 liters of glucose and saline solution was given with the extract, one cannot say that the latter was the effective agent. A Kepler-Power² water test was done. In adrenal insufficiency there is a tendency for the urea to be higher in the blood than in the urine. Patients with Addison's disease do not have good diuresis following water injection. The ketosteroids are interesting—they were low, but a good many patients have low ketosteroid excretion. If the ketosteroids are normal, one can immediately rule out Addison's disease. If low, in any patient who is hospitalized and sick, one cannot prove Addison's disease. The prothrombin time was normal. The cephalin flocculation test was normal. These constitute evidence against a severe grade of hepatitis.

The patient went home for two or three days, became listless, with a feeling of impending death, came to the hospital in extremis, had a temperature of 101°F. and died. Just before the final episode she became alert enough to respond when glucose and adrenocortical extract were given intravenously. That merely suggests, to my mind, the hydrating effects of glucose, especially a temporary improvement of the cerebral state so that she could realize where she was. Although there are a considerable number of points in favor of adrenal insufficiency, I hesitate to make that diagnosis in this patient because of several points: the presence of hydrochloric acid in the stomach, the +++ test for acetone in the urine and the disproportion between the chloride and sodium levels. The pigmentation is compatible, the excretion of ketosteroids is compatible, and the glucose-tolerance test and the clinical course fit in with many cases. I do not believe that she had Addison's disease before heavy metals were administered; if so, she would have had a much severer reaction.

Regarding hepatitis, I think that the patient had evidence of liver damage, but that it was not sufficient to cause death. She must have had a considerable amount of functioning liver tissue to have a +++ test for acetone in the urine.

Regarding the possibility of a renal lesion, arsenphenamine and bismuth might have caused it. There was evidence of tubular degeneration, but the final urine had a specific gravity of 1.018, with only a few casts. So far as the urine findings alone are concerned, one cannot say that she had nephrosis, but the response to sodium and chloride—the prompt rise in chloride and the slower drop in sodium—and the fact that the sodium chloride levels could be maintained on the intravenous fluid alone strongly suggest difficulty in sodium and chloride excretion on the part of the kidneys.

The blood pressure was low, and the pulse rate was rapid. I suppose that there were small areas of focal myocarditis and swelling of the myocardial muscle fibers. As a terminal event she may have had heart failure or even a pulmonary infarct. She had definite evidence of a terminal change in the brain, as demonstrated by the paralysis. I am a little disturbed with respect to the bone marrow. She may have had some depression of the bone marrow, because the final counts were lower than the earlier ones, but the bone-marrow depression was not marked.

Am I permitted to see the heart films? I should like to know whether the heart was small or normal.

DR. LAURENCE L. ROBBINS: It is certainly small, although many normal people have hearts of this size. This was taken in the Out Patient Department one year before the first admission.

DR. THORN: There was no subsequent change in the heart size?

DR. ROBBINS: No. The second film was taken three months before the first admission and showed no change. We have no later films.

DR. THORN: A small heart is consistent with adrenal insufficiency and certainly against extensive myocardial change, and against anything in the way of renal lesion. It almost makes me change my mind in this case.

If the heart became definitely larger, one would consider a myocardial or renal defect. If the heart remained small, one would certainly make a diagnosis of adrenal insufficiency. The heart size is one of the most important things to follow in a patient with adrenal insufficiency. One can tell more about the state of the circulation from the size of the heart than from any other factor. I must add to my diagnosis the question of Addison's disease.

DR. OLIVER COPE: In contrast to clinical observations, there is no change in the output of hydrochloric acid in the stomach in experimental adrenal insufficiency. In the surgical research laboratories of this hospital the dog has been observed to secrete hydrochloric acid (pH 0.85) throughout the development of acute adrenal insufficiency, even terminally.

It is, to my mind, entirely a matter of stimulation, which is difficult to obtain in the dog. The patient with Addison's disease also has anorexia and vomiting. When the dog is fed artificially by stomach tube it puts out hydrochloric acid even with a blood chloride level below 80 milliequiv. To my mind, therefore, the presence of hydrochloric acid in the stomach of a patient does not exclude adrenocortical insufficiency.

DR. JACOB LERMAN: When this patient was first admitted, the diagnosis was arsphenamine jaundice or hepatitis. The resident who saw her on various occasions, Dr. Gordon S. Myers, raised the question of Addison's disease because of the peculiar pigmentation in the mouth, plus the low salt in the blood. He thought that the appearance was different from that of bismuth poisoning. That argument went on pro and con between the residents, the interns and the visiting staff for some time, and finally the consensus was swayed against Addison's disease, primarily because of the presence of ketosteroids in the urine. The opinion was that any amount of ketosteroids militated against a diagnosis of Addison's disease.

I saw her when she came in the second time. The jaundice had cleared completely, and to me, the picture looked quite characteristic of Addison's disease, with a typical distribution of pigmentation. She was in collapse but responded readily to salt and adrenocortical extracts. We speculated whether bismuth poisoning can play a role in the production of Addison's disease. In the experience of a large syphilitic clinic where large doses of bismuth are given over many years it is extremely rare to find a case of Addison's disease. I therefore threw out bismuth as a factor.

We were particularly convinced of the diagnosis of Addison's disease when she returned in coma and died quickly. Because she had responded at first so quickly to small amounts of adrenocortical extract and of salt intravenously, we thought that she had a mild case of Addison's disease. The various members who saw her believed that the proper treatment was to carry her along on salt and to give extract as indicated. Apparently she was in a much severer stage of the disease than we had anticipated.

CLINICAL DIAGNOSIS

Addison's disease.

DR. THORN'S DIAGNOSES

Healed arsphenamine hepatitis.

Myocardial failure.

Pulmonary infarct.

Tubular changes in kidney (bismuth)?

Addison's disease?

ANATOMICAL DIAGNOSES

Addison's disease.

Tuberculosis of adrenals, bilateral.

Tuberculosis of mesenteric lymph nodes.
Pericarditis, acute fibrinous, with effusion.
Pulmonary edema.
Hydrothorax, bilateral.
Ascites.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Autopsy showed that both adrenal glands were three to four times their normal size, and completely replaced by caseous tuberculosis. The regional nodes were caseous, and there was old tuberculosis in the lungs, both apices being completely scarred. The immediate cause of death was an acute pericarditis with effusion. It is perhaps fortunate for Dr. Thorn that chest films were not taken at the time of the last admission, because the effusion would have caused an enlarged heart shadow. The heart itself was extremely small.

DR. THORN: I have seen six cases of Addison's disease with pericarditis. In one or two of them it was hemorrhagic.

DR. COPE: In these cases was the etiologic agent a streptococcus?

DR. THORN: No cultures were done, and no organisms were seen on smear.

DR. CASTLEMAN: The liver was normal in size, perhaps a bit small, and showed no evidence of hepatitis. The kidneys were essentially normal. We found no anatomic lesions of syphilis.

DR. THORN: The acetone is the most interesting aspect of this case. It is unusual for the urine of a patient with adrenal insufficiency to give a ++++ test. Differential diagnosis could have been made on the response to desoxycorticosterone acetate rather than to sodium chloride, since the latter is nonspecific and helpful in many types of dehydration, whereas the hormone effect is specific.

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CASE 30232

PRESENTATION OF CASE

A sixty-three-year-old night watchman entered the hospital because of cramps in the lower abdomen of five days' duration.

During the year preceding entry, the patient had noticed occasional cramps in the lower abdomen, increasing constipation without melena, slight decrease in the size of the stools and slight weight loss. Five days prior to admission he developed persistent cramps in the lower abdomen and anorexia. He had no bowel movements for the three days preceding entry, except for a small one on the morning of admission. During this time, however, he had

passed gas by rectum but had been aware of increasing retention of gas and distention

Physical examination showed a well-developed, slender man in no discomfort. The heart and lungs were normal. The abdomen was distended and tympanic. Intermittent, high-pitched, peristaltic rushes were heard. A large tympanic, nontender mass was present in the cecal area. Rectal examina-

tion showed the cecum was somewhat dilated. Proctoscopy, including the rectum and sigmoid to a point 20 cm above the anal sphincter, was negative.

On the second hospital day a cecostomy was done. Postoperatively the patient did well. On the third hospital day a barium enema showed a mass in the pelvis, displacing the rectum and sigmoid to the left. The examination was unsatisfactory because of the



FIGURE 1 Post-Evacuation Film following a Barium Enema
The small arrow points to the lesion in the sigmoid, the large arrow, to barium in the cecum

tion showed a soft palpable mass 7 cm above the anus

The blood pressure was 148 systolic, 72 diastolic. The temperature was 98.6°F, the pulse 100, and the respirations 24.

Examination of the blood showed a red-cell count of 4,480,000 and a white-cell count of 10,450. The urine was normal. A blood Hinton test was negative. The stools gave a ++ guaiac test. A plain film of the abdomen showed a large amount of gas in the colon, extending to the lower sigmoid. The

large amount of gas in the colon. A Miller-Abbott tube was passed. A repeat barium enema showed an annular area of narrowing, extending over a distance of approximately 6 cm, and situated about 3 cm proximal to the rectosigmoid junction. The margins were shelf-like, and there was ulceration. During fluoroscopic examination only a small amount of barium passed beyond the tumor. After the patient had evacuated some of the barium, the films showed that considerable barium had passed into the descending colon, and there was barium

in the small intestine (Fig. 1). A mass was present in the right side of the pelvis that displaced the rectum rather markedly to the left.

On the fourteenth hospital day a transverse colostomy was performed. This was opened two days later. There was excellent drainage. Irrigation to the loops was satisfactory. During the course of the next two weeks the patient's general condition improved considerably and he felt and looked much better. On the thirtieth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. E. PARKER HAYDEN: From the beginning this seems to be a typical story of progressive, large-bowel obstruction—a story of increasing constipation and cramps in the lower abdomen over a period of a year, with slight decrease in the size of the stools. The record states that no blood had been noted. One thinks naturally of the two commonest diseases that obstruct the large bowel in a person of this age: carcinoma and diverticulitis. The lack of blood makes one think of diverticulitis. On the other hand, this man had had a slight weight loss, suggesting cancer. There was also the five-day episode of pronounced obstruction, which brought about his entry to the hospital, and the period of three days in which he had had no movement except one small one, but was passing gas by rectum.

On physical examination the patient was described as being sallow, and he had a distended, tympanitic abdomen, with high-pitched peristalsis, suggesting an obstructing lesion based not on inflammation but on a mechanical obstruction somewhere in the colon. In diverticulitis there is, of course, a localized inflammatory process, but the resulting obstructive symptoms are mechanical in nature. There is blocking of the lumen, owing to swelling of the bowel segment, and a real mechanical obstruction develops. The finding that is most difficult to explain is the tympanitic nontender mass in the cecal area. I suppose we can fairly well rule out a distended bladder because of tympany and the location of the mass on the right side.

The first diagnosis that occurs to me in this case is an old appendiceal abscess with sufficient putrefaction in the abscess to produce gas. Now and then a large abscess is tympanitic to percussion, and it may not be tender if it has been present for a long while. On the other hand, since the man had no fever and no increased white-cell count, an abscess seems unlikely.

The man may have had some queer intraperitoneal herniation. I can recall a patient who would fit this description rather well. She had a herniation of the small bowel through an aperture around the cecum, producing a similar picture—a large, freely movable, tympanitic, soft mass in the right lower quadrant. I have never seen one since, but the

memory of this one came quickly to mind. This man could have had an intraperitoneal herniation. On the other hand, such a lesion would probably have involved the small bowel, and in that case one would expect symptoms of small-bowel, rather than large-bowel, obstruction. Furthermore, a Miller-Abbott tube was passed.

Another possible explanation is a volvulus of the right colon, which can produce a large tympanitic mass in that area. Yet we have evidence of a definite lesion in the upper sigmoid. If this lesion was 3 cm. proximal to the rectosigmoid junction, it should have been visualized when the proctoscope was passed 20 cm., but one must make allowances for a discrepancy in the estimated distance.

The description of the barium-enema examination, which showed a constricting lesion with shelf-like margins and ulceration, makes it difficult to conclude that this was anything except carcinoma of the descending colon. If there was a carcinoma of the descending colon, this, rather than the appendix, could have perforated and could have produced a big abscess.

One should also consider the possibility of some sort of cyst in the right lower quadrant or pelvis. In other words, the cecal mass may be one of the familiar red herrings that crop up so often in these conferences, and that have nothing to do with the principal diagnosis.

I shall conclude by saying that this woman had a carcinoma of the descending colon. This seems evident from the x-ray description and from what we know about the operative procedures. When one does a cecostomy, it is usually for large-bowel obstruction, although I have seen the operation performed when that did not exist. A transverse colostomy, coming later, suggests that the operator found something in the left colon which he thought he could resect, with an anastomosis. So, influenced by these facts, I think I must make a diagnosis of carcinoma of the descending colon, with acute obstruction of five days' duration. I have no idea what the soft mass was. The diagnosis that fits this picture best is some type of intraperitoneal herniation.

DR. BENJAMIN CASTLEMAN: Would you like to see the x-ray films?

DR. HAYDEN: Yes.

DR. MILFORD SCHULZ: The most pertinent ones were made following cecostomy.

DR. HAYDEN: I intended to emphasize the fact that, since the Miller-Abbott tube was used, obstruction in the small bowel seems likely.

DR. SCHULZ: Curiously enough the lesion shows best in the routine films rather than in the spot films. There is something peculiar down here. There are several collections of barium that do not seem to be in the colon.

DR. HAYDEN: That suggests perforation, with a large abscess cavity and gas.

CLINICAL DIAGNOSIS

Carcinoma of sigmoid, with ileocolic fistula.

DR. HAYDEN'S DIAGNOSIS

Carcinoma of descending colon, with obstruction and perforation.

Intraperitoneal small-bowel hernia?

ANATOMICAL DIAGNOSIS

Adenocarcinoma (Grade III) of sigmoid, with
• ileosigmoidal fistula.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At operation the surgeon felt a large mass in the region of the descending colon that was adherent to loops of small bowel. He was able to separate a few of the loops of small bowel from the mass, but suspecting an ileocolic fistula because of the presence of barium in the small intestine as demonstrated by the x-ray films, he resected the colon and the adjacent small intestine.

We found an annular, 5-cm., ulcerating carcinoma of the sigmoid, which had extended through the serosa and communicated with the ileum by means of a fistulous tract 1.5 cm. long and about 2 mm. in diameter. No cancer was present in the small intestine.

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ONE HUNDRED AND SIXTY-THIRD ANNIVERSARY

THE one hundred and sixty-third anniversary of the Massachusetts Medical Society, held at the Hotel Statler, Boston, on May 22, 23 and 24, proved to be the most successful meeting ever held. Although the total registration — 1440 — was somewhat less than the 1556 members who attended in 1942, it is obvious that the former figure represents a higher percentage of members practicing within the Commonwealth than does the number of two years ago, owing to the absence of approximately 1500 members because of military service.

At the annual meeting of the Council, several matters of general interest were discussed, and appropriate action was taken. The Committee on Membership submitted an exhaustive report covering the admission of graduates of foreign medical schools to the Society; on the basis of this study, the committee stated that no change in the by-laws was indicated, and this recommendation was approved by the Council. The Subcommittee to Meet with the Medical Advisory Committee of the Industrial Accident Board reported that arrangements had been made with insurance companies whereby physicians will be reimbursed for emergency medical care and that it is permissible for a patient to be moved to another hospital where he can be cared for by a physician of his own choice, provided there is assurance that the care will be adequate. The War Participation Committee stated that a program designed to take care of any catastrophic emergency — war or civilian — had been worked out as a co-operative venture by the Society, the American Red Cross and the Massachusetts Committee on Public Safety. After considerable discussion, it was voted to hold over the recommendations of the Postwar Loan Fund Committee until the February meeting of the Council, the consensus being that the reaction of the Society as a whole should be obtained before taking action. Dr. Reginald Fitz, Massachusetts chairman of the Procurement and Assignment Service, reported that approximately 2900 physicians coming under the jurisdiction of his committee were serving with the armed forces, that there had been little evidence of shortage of physicians, that the 9-9-9 plan for interns and residents was functioning satisfactorily and that, by and large, the medical manpower situation had become clarified and well adjusted. On the basis of recommendations by the Committee on a Medical Information Bureau, the Council voted to establish such a bureau at the headquarters of the Society, to appoint a committee to supervise the activities of the bureau and to appropriate the sum of \$2500 for the annual maintenance of the bureau. And, finally, the appointment of the Postwar Planning Committee was authorized. The officers elected for the current year are as follows: president, Elmer S. Bagnall; vice-president, Sumner H. Remick;

sident-elect, Reginald Fitz; secretary, Michael Tighe; treasurer, Eliot Hubbard, Jr.; assistant treasurer, Norman A. Welch; and orator, Frank H. Key.

At the annual meeting of the Society, Dr. William Robey presented an appreciation of the late treasurer, Charles S. Butler, and the president, Dr. I. Lee, reported on the state of the Society. At the close of the meeting, the orator, Joseph C. Key, delivered the annual oration, entitled "A Major Factor in Experimental Traumatic Shock," which will appear in a subsequent issue of the Journal.

The annual dinner was well attended, nearly 500 tickets having been sold. The Honorable Leverett Stettin, Governor of Massachusetts, took the occasion somewhat to task for its failure to make laymen aware of all that physicians have done and are doing for the public good; he warned that efforts to provide good medical care at a reasonable cost must be provided. Bill Cunningham, with his customary forceful style, pleaded for better morale at the home front.

Many excellent papers were presented at the various scientific sessions, and the Shattuck Lecture given by Dr. Alfred Blalock, surgeon-in-chief, at Hopkins Hospital, and professor of surgery, at Hopkins University School of Medicine, the subject being "A Consideration of Certain Recent Advances in Surgery."

The luncheon meetings of the sections were extremely popular; in fact at that of the Section of Medicine the demand to hear the speaker, Dr. Peter C. Alvarez, of the Mayo Clinic, was so great that the meeting had to be moved from Parlor B to the Georgian Room.

The scientific and technical exhibits were so numerous that the Mezzanine, as well as the Ballroom and Ballroom Assembly, was filled to capacity. Receipts from the rental of booths made an all-time record, a fact that will undoubtedly receive favorable comment from the Treasurer and the Committee on Finance.

Once again, the Society is greatly indebted to Gordon M. Morrison and his committee, as well as to Robert St. B. Boyd, the executive secretary.

NEWTON HEALTH DEPARTMENT AGAIN WINS AWARD

NEWTON has again received honors for attaining excellence in protecting public health in wartime by being one of the fifty-three cities and counties to receive recognition in the 1943 National Health Honor Roll. The program was sponsored by the United States Chamber of Commerce and the American Public Health Association.

The winners were selected by leading national authorities, who spent weeks grading the reports of participating communities throughout the country. Emphasis was placed on specific measures to control communicable diseases, such as venereal disease, tuberculosis and children's diseases. Sanitation, including protection of milk and food supplies, proper safeguards for maternity care, child health and welfare, effective health education, adequate measures to promote industrial health and other health services were also given primary consideration. Many of the participating communities were war-production centers that have found it necessary to make an inventory of health conditions regarding both wartime health problems and postwar planning.

In commending the winning communities as well as those that participated in the program, the United States Chamber of Commerce said:

This achievement deserves the highest praise and support and reflects great credit on the health officers, officials, voluntary health organizations, chambers of commerce and other business and civic groups in these localities for giving adequate attention to the wartime health of war workers and citizens.

It is our hope that the records of the 1943 National Health Honor Roll cities and communities will be an incentive and guide to others to build up their health protection services. We hold this an essential home-front contribution to speed the winning of the war and to meet the great problems of postwar readjustment.

The evaluation schedule used in this national program is one of the best possible tools for post-war planning. Its use gives every community exact knowledge of where it stands in health and hospital facilities in connection with adjusting itself to post-war conditions. Communities that make this inventory now are steps ahead of other communities in postwar planning. Armed with definite plans for improvements and expansion, these communities will obviously be in the best position to obtain trained technicians and additional facilities for improving their health programs after the war.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

COOK — Edward M. Cook, M.D., of York Harbor, Maine, died May 20. He was in his forty-sixth year. Dr. Cook received his degree from Tufts College Medical School in 1924. He was a member of the American Medical Association.

His widow, his mother and a son survive.

FLAGG — Harry H. Flagg, M.D., of Charlestown, died May 25. He was in his sixty-fourth year.

Dr. Flagg received his degree from Tufts College Medical School in 1908. He was a member of the American Medical Association and the Charlestown Medical Society.

His widow and two daughters survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

REGULATIONS REGARDING GONORRHEA REVISED

The regulations of the Massachusetts Department of Public Health regarding venereal diseases have recently been revised. Among other changes the regulations have been made applicable to chancroid, granuloma inguinale and lymphogranuloma venereum.

One other change has been the adding of a new paragraph, which reads as follows:

Minimum Requirement for a Negative Diagnosis in Women Who Are Suspected of Having a Gonococcal Infection. Whenever a female is alleged to have been exposed to gonorrhea, or to have been the source of infection of gonorrhea, the department shall require that there be one or more negative cultures of material taken from the urethra and cervical canal, in accordance with the instructions accompanying the outfit, before the department will accept a report that the person is free from infection; said cultures to be done in a laboratory approved by the department.

(NOTE. If, in the physician's judgment, there exists a history of exposure and/or physical signs and symptoms of the disease in the female, regardless of negative laboratory findings, the case should be reported as gonorrhea.)

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR APRIL, 1944

RÉSUMÉ

DISEASES	APRIL 1944	APRIL 1943	SEVEN-YEAR MEDIAN
Anterior poliomyelitis.....	1	3	1
Chancroid	1	*	*
Chicken pox	2792	1136	1286
Diphtheria	19	8	11
Dog bite	920	949	959
Dysentery, bacillary	0	2	7
German measles	397	8658	157
Gonorrhea	319	379	368
Lymphogranuloma venereum	7	*	*
Measles	3490	7282	4012
Meningitis, meningococcal	54	118	7
Meningitis, Pfeiffer-bacillus	4	1	7
Meningitis, pneumococcal	7	5	14
Meningitis, staphylococcal	1	—	†
Meningitis, streptococcal	2	2	†
Meningitis, other forms	2	5	†
Meningitis, undetermined	8	15	†
Mumps	1483	770	785
Pneumonia, lobar	332	360	521
Salmonella infections	5	42	6
Scarlet fever	1737	2579	1172
Syphilis	334	455	479
Tuberculosis, pulmonary	196	253	253
Tuberculosis, other forms	19	17	25
Typhoid fever	4	3	3
Undulant fever	3	3	3
Whooping cough	312	604	798

*Made reportable in December, 1943.

†Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

COMMENT

Diphtheria showed a distinct downward tendency in April although running far ahead of the same month last year. The cases were almost entirely confined to the eastern end of the Commonwealth. Meningococcal meningitis, pleasingly enough, showed a figure less than half that of last April. But it was still nearly eight times the seven-year median.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from: Amherst, 1; total, 1.

Diphtheria was reported from: Boston, 7; Brockton, 1; Chelmsford, 1; Fitchburg, 2; Lawrence, 4; Lexington, 1; New Bedford, 1; Salem, 1; Somerville, 1; total, 19.

Encephalitis, infectious, was reported from: Longmeadow, 1; total, 1.

Malaria was reported from: Boston, 15; Camp Edwards, 10; Cushing General Hospital, 3; Fort Banks, 20; Fort Devens, 15; Fort Rodman, 3; Haverhill, 1; Swansea, 1; total, 68.

Meningitis,, was reported from: Acton, 1; Adams, 1; Andover, 1; Ashland, 1; Boston, 12; Bridgewater, 1; Brockton, 1; Cambridge, 1; Camp Edwards, 2; Carver, 1; Charlton, 1; Chelmsford, 1; Easthampton, 1; Fall River, 2; Fort Devens, 1; Framingham, 1; Greenfield, 1; Lowell, 2; Marlboro, 1; Medford, 1; Newton, 1; North Attleboro, 1; Northampton, 1; Norton, 1; Plymouth, 1; Reading, 1; Salem, 1; Somerville, 1; Springfield, 1; Swansea, 1; Wakefield, 1; Waltham, 1; Watertown, 1; Webster, 1; Weymouth, 1; Winthrop, 1; Woburn, 2; Worcester, 1; total, 54.

Meningitis, Pfeiffer-bacillus, was reported from: Boston, 1; Brockton, 1; Framingham, 1; Peabody, 1; total, 4.

Meningitis, pneumococcal, was reported from: Holyoke, 1; Lynn, 1; Melrose, 1; Quincy, 1; Springfield, 1; Sutton, 1; Westport, 1; total, 7.

Meningitis, staphylococcal, was reported from: Boston, 1; total, 1.

Meningitis, streptococcal, was reported from: Boston, 2; total, 2.

Meningitis, other forms, was reported from: Rockland, 1; (leptomeningitis) Springfield, 1; (leptomeningitis) Somerville, 1; total, 3.

Meningitis, undetermined, was reported from: Boston, 1; Lowell, 1; Ludlow, 1; Norwell, 1; Paxton, 1; Springfield, 2; Worcester, 1; total, 8.

Salmonella infections were reported from: Boston, 1; Cambridge, 1; Newton, 3; total, 5.

Septic sore throat was reported from: Billerica, 2; Boston, 9; Camp Edwards, 1; Fall River, 1; Haverhill, 1; Hull, 1; Greenfield, 1; Mansfield, 1; Upton, 1; Williamstown, 2; total, 20.

Tetanus was reported from: Hanover, 1; total, 1.

Trichinosis was reported from: Concord, 3; Hadley, 1; total, 4.

Typhoid fever was reported from: Chicopee, 1; Melrose, 1; Quincy, 1; Springfield, 1; total, 4.

Undulant fever was reported from: Cushing General Hospital, 1; Hopedale, 1; Millbury, 1; total, 3.

MISCELLANY

INTRAPLEURAL PNEUMONOLYSIS

The emphasis on early diagnosis of pulmonary tuberculosis would seem to be wasted if effective treatment is unnecessarily postponed. Discriminating selection of cases for collapse therapy, skillful choosing of the appropriate method and prompt employment of the elected procedure are indicated in the interest of all concerned. Pertinent facts are brought out in a recent article (Dailey, J. E. Intrapleural pneumonolysis. *Dis. of Chest* 9: 492-495, 1943), which is abstracted below:

It seems generally agreed that at least half the cases of pulmonary tuberculosis require some form of collapse treatment, either reversible or irreversible. Thoracoplasty is the best surgical example of the latter, while the oldest technique devised—pneumothorax—is a good representative of temporary, reversible collapse of the lung.

The chest specialist is the one to select either method after he has evaluated the patient's condition and the stage of his pneumonitis. The mistaken belief that "time heals everything" must give way to acknowledgment that this disease invariably demands immediate consideration and active methods of treatment whenever indicated. In this race against time, the presence of a cavity calls for measures to avert it before delay invites a hemorrhage or spread of infection in a hopeless condition.

Pneumothorax remains the first choice, but is successful only about half the cases in which it is initially tried. Lack of success may be attributed to adherence of the two pleural faces so that collapse of the cavity is impossible or incomplete. Delay in the institution of pneumothorax may be due to the parenchymal inflammation to progress and involve the pleura until adhesions form and so defeat later attempts what should have been a simple collapse procedure.

Formerly, a risky method attempted to stretch or break adhesions by forcing air into the pleural cavity under positive pressures. Serious complications developed if the pressure breaking off near the lung, tore the latter so that a septic or mixed infection empyema resulted. Serious hemorrhage might follow rupture of a sizeable vessel incorporated in the adhesion. Precious time was often wasted while the hoped for stretching of the adhesion was awaited, meanwhile the still unaffected cavity might supply bacilli to the other cavities elsewhere.

Intrapleural pneumonolysis was designed to transform, where feasible a poor pneumothorax result into a satisfactory effective collapse. Under local procaine infiltration anesthesia a special cannula is introduced between the ribs or the pleural space, transmitting a visual instrument not like a cystoscope. Through this the operator views the error and by means of a cautery inserted through a second cannula in another interspace severs the adhesions under direct vision.

Adhesions vary in size and shape and may be multiple, ranging from "fiddle string" to short, thick and cylindrical, may resemble accordion-pleated sheets that radiate in all directions and run all the way from paper-thinness up to one or several centimeters in diameter. In using the cautery it is necessary to remember that thicker adhesions contain lung tissue or large blood vessels and that they are attached firmly to the aorta, subclavian artery or other mediastinal structures. Great skill is required to avoid tearing similar to those already listed above as chargeable stretching and rupture of adhesions.

A skilled operator severs an adhesion as near its parietal extremity as possible, thus protecting the lung while exercising due caution as regards the intercostal structures as well, especially if actual dissection in the latter area proves necessary. In competent hands, backed by adequate experience and judgment when and when not to cut, the operation is a minimal one as regards the patient's discomfort. In less experienced hands, however, it can present dangers exceeding those of almost any other major intrathoracic surgical procedure.

When a pneumothorax is started and adhesions can be seen to interfere with collapse, provided the space is large enough for the surgeon to manipulate his instruments, there is no reason for delay. Besides the well known hazards of an open cavity, the longer one waits the thicker grows the pleura, increasing the bands and the greater the difficulty of cutting them.

Very large adhesions are often partially attached to the chest wall, and may be widespread to the point of being impossible to remove without the risk of the unsuccessful.

Pneumothorax and the selection at once of a collapse procedure other than pneumonolysis.

Summary: Remember the time factor and begin active pneumothorax treatment immediately in any patient who has a cavity. Don't wait to see what happens to the case with prolonged bed rest. Too often the realization will be accompanied by disappointment and chagrin.

In about half the cases a pneumothorax will be complicated by adhesions.

Don't attempt to stretch adhesions by means of a positive pressure pneumothorax.

Make an attempt to sever them by intrapleural pneumonolysis—again remembering the importance of time—as soon as possible.

In the hands of an expert, the unfavorable consequences of the operation are insignificant and the complications rare, but when performed by one with little experience, the dangers are very real.

If it is impossible to improve the collapse by pneumonolysis, abandon the pneumothorax and perform a thoracoplasty. — Reprinted from *Tuberculosis Abstracts* (May, 1944).

NOTE

Several appointments to the faculty of Tufts College Medical School have been recently announced. Dr. Norman A. Welch, physician in chief at the Carney Hospital, was named professor of clinical medicine. Mr. Manfred Bowditch, director of the Division of Occupational Hygiene, Massachusetts Department of Labor and Industries, was appointed professor of industrial hygiene. Dr. Walter T. Garfield was designated as emeritus professor of dermatology, with Dr. John G. Downing, physician in chief of diseases of the skin, Boston City Hospital, succeeding him. Dr. Raymond D. Adams, neuropathologist at the Boston City Hospital, was named lecturer in neurology.

CORRESPONDENCE

RESTORATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held May 17, the Board voted to restore the license to practice medicine in this Commonwealth of Dr. David S. Goodman, 168 Chestnut Street, Chelsea.

H. QUIMBY GALLUP, M.D., Secretary
Board of Registration in Medicine

State House
Boston

NOTICE FOR NAVAL MEDICAL OFFICERS

To the Editor: A total of 100 qualified physicians and dentists are needed by the Bureau of Medicine and Surgery for assignment to the United States Veterans Administration. The program is open to males not over sixty years of age. Except for those specially nominated by the United States Veterans Administration rank will be comparable with age and experience. The physical requirements are the same as those established for general appointments, but special waivers may be granted. No indoctrination period is required. Those selected will be assigned to the United States Veterans Administration and physicians and dentists now thus employed will be assigned, if commissioned, to the Veterans Administration.

It is to be emphasized that the procurement of physicians and dentists for regular service in the Navy is still urgent. Recommendation for this special program will be given only in those cases in which a doctor or dentist is over age, or where a waiver of physical defects not ordinarily granted is required.

As in the case of all medical and dental officer applications, a statement of availability by the Procurement and Assignment Service is required.

H. S. GLIDEN
Commander MC-V(G), USNR
Senior Medical Officer

Office of Naval Officer Assignment
150 Causeway Street
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MEDICAL FEES IN RURAL VERMONT

To the Editor: A study of farm economies in Vermont has recently been published (Adams, T. M. *Prices Paid by Vermont Farmers for Goods and Services and Received by Them for Farm Products, 1790-1940, 11 pages of Vermont Farm Labor, for Farm Products, 1790-1940, 11 pages of Vermont Farm Labor, 1790-1940* 176 pp. Bulletin 507, University of Vermont and State Agricultural College, Burlington, Vermont 1944). The sources are account books of individuals and business firms in various rural communities of the state. Vermont has the largest rural percentage of population of any state in New England. In 1940 66 per cent of the people of Vermont were in communities of less than 2,500 population whereas in Massachusetts only 11 per cent lived in rural areas, and in Rhode Island only 8 per cent.

Four fifths of the towns in the state were covered in the search for account books of individuals and business firms.

Four tons of such books and diaries were consulted. The compiler is a member of the faculty of the University of Vermont, and this study was accepted by Cornell University as a thesis for the degree of Doctor of Philosophy.

One of the one hundred and twenty-three lists of prices is that of medical fees from 1800 to 1940, for which a table with eight hundred and forty-six entries appears on pages 58-60. I have abbreviated this table to forty-five entries by taking only the decennial years and only the fees for three types of medical service, namely, an office call, a house visit by day within one mile and an obstetric delivery. The list is as follows:

DATE	OFFICE CALL	HOUSE VISIT	OBSTETRIC DELIVERY
1800		\$0.25	\$2.00
1810	\$0.30	0.45	2.00
1820	0.30	0.45	3.00
1830	0.28	0.41	2.83
1840	0.30	0.46	3.12
1850	0.42	0.50	3.00
1860	0.42	0.50	3.00
1870	0.67	0.83	5.00
1880	0.62	0.75	5.00
1890	0.56	0.81	5.00
1900	0.54	0.88	6.14
1910	0.72	1.20	9.75
1920	1.29	1.89	20.00
1930	1.34	2.03	22.44
1940	1.34	2.03	23.15

The table does not give an entry for an office call in 1800. Account books of physicians in eastern New York, which I possess, show that when the fee for a house visit was 25 cents in the early nineteenth century, the average fee for an office call was 18 $\frac{3}{4}$ cents. Assuming that the same relation held in neighboring Vermont, the total for the three services was \$2.44 in 1800. This total did not double until 1865, and it trebled in 1900. In 1905 the total became four times the original and in 1912 five times the original. In 1925 it first passed ten times the original, and in 1940 it was nearly eleven times what it was in 1800. It is evident that fees in rural medical practice in Vermont increased much more rapidly in the twentieth century than in the nineteenth century. No mileage was charged for a visit within one mile, but rural physicians were accustomed to charge mileage for professional visits at a distance of more than one mile. The rate in Vermont in 1800 was in accord with that in other northern states, being 10 cents per mile. In 1865 the rate became approximately 20 cents, in 1900 approximately 25 cents, in 1916 approximately 30 cents, and in 1925 approximately 35 cents. The fees did not include medicine during the greater part of the nineteenth century; pharmacies were rare except in cities, and the physician furnished the medicines for his patients, for which he made an additional and separate charge. The prices entered in the table are the average from the account books of physicians in each year. The number available varied but was enough to give a fair cross section.

FREDERICK C. WAITE, Ph.D.

Dover, New Hampshire

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Hundred Years of Medicine. By C. D. Haagensen, M.D.; and Wyndham E. B. Lloyd. 8°, cloth, 444 pp., with 42 illustrations. New York: Sheridan House, 1943. \$3.75.

This is a story of the medical discoveries of the past century, written in simple terms for the layman. The various diseases and conditions are considered individually, and the work of outstanding figures, such as Virchow, Semmelweis, Koch, Pasteur, Lister, Ehrlich, Röntgen, Halsted, Cushing, Banting, Minot and Domagk, are emphasized. A bibliography for students is to be found at the end of the work, and the text is well illustrated.

Blood Supply of the Visual Pathway. By Calvin M. Kershner, M.D., M.S. (ophth.). 8°, cloth, 160 pp., with 33 illustrations. Boston: Meador Publishing Company, 1943. \$3.00.

This small monograph attempts to gather together in one place in a systematic manner the essential facts displayed in a wide literature, so as to make the anatomical knowledge of value to the ophthalmologist. The work is divided into two parts. In the first, the general arterial supply and the general venous drainage are considered. In part two there are detailed descriptions of the blood supply and drainage of each section of the visual pathway.

Clinical Diagnosis by Laboratory Examinations. By John A. Kolmer, M.S., M.D., Dr.P.H., Sc.D., LL.D., L.H.D., professor of medicine, School of Medicine and School of Dentistry, Temple University, and director, Research Institute of Cutaneous Medicine. 8°, cloth, 1239 pp., with 75 illustrations. New York: D. Appleton-Century Company, 1943. \$8.00.

This new work aims to represent fully the clinical interpretations of laboratory examinations and their practical applications in the diagnosis of disease, with a special section on technical methods sufficient for meeting the needs of teaching clinical pathology to medical and dental students. It is divided into three parts: laboratory examinations, divided into twenty-one chapters; the practical applications of laboratory examinations in clinical diagnosis, consisting of twelve chapters; and the techniques of laboratory examinations, divided into nine chapters.

Veterinary Bacteriology. By Ival A. Merchant, D.V.M., Ph.D., C.P.H., associate professor of veterinary bacteriology and hygiene, Iowa State College. Second edition. 8°, cloth, 640 pp., with 135 illustrations. Ames, Iowa: The Iowa State College Press, 1942. \$6.50.

The second edition of this book has not been extensively revised, because of the exigencies of wartime. The chapter on the genus *Streptococcus* has been changed more extensively than any other. The fact that the first edition was published in September, 1940, and the second edition in November, 1942, speaks well for the popularity of the work.

The Biochemistry of Malignant Tumors. By Kurt Stern, M.D.; and Robert Willheim, M.D., professor, University of Philippines, Manila. 8°, cloth, 951 pp. Brooklyn, N. Y.: Reference Press, 1943. \$12.00.

This special work attempts to cover the relation of cancer to chemistry in the broadest meaning of both words, based on a collection of literature as complete as possible. It is the first publication in English of a treatise on the subject. The arrangement of the material is in line with the general principles of biochemistry. The main emphasis has been placed on the work of the last twenty-five years, and the literature has been systematically covered until the end of 1941. In 1936 the authors published in Vienna a German work of the same character and this book is an amplification of that monograph. Most of the views expressed were formed during a period of more than ten years of joint experimental work in cancer research. Considering the work of others in the field of cancer research, the authors have endeavored to enumerate the facts and also to introduce a critical analysis.

White Blood Cell Differential Tables. By Theodore R. Waugh, M.D., C.M., pathologist-in-chief, Royal Victoria Hospital, associate professor of pathology, McGill University, and consulting pathologist, Montreal Homeopathic Hospital, Montreal, Quebec. 12°, cloth, 126 pp. New York: D. Appleton-Century Company, Incorporated, 1943. \$1.60.

Ninety per cent of the space of this small pamphlet is given up to tables for computing rapidly from the differential percentages the number of each type of white blood cell per cubic millimeter of blood. The tables cover the numbers up to 10,000. Preceding the tables there are 15 pages of preliminary descriptive matter.

(Notices on page xi)

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THE TREATMENT OF ANURIA*

CHARLES W. STYRON, M.D.,† AND WYLAND F. LEADBETTER, M.D.‡

BOSTON

THE early determination of the etiology of urinary suppression is frequently lifesaving and successful therapy depends largely on clinical evaluation of a case in the first few hours of observation. Ordinary routine treatment should be altered to meet the features in a particular case. Though the division into medical and surgical problems is necessary and helpful, a more descriptive classification is that of obstructive and nonobstructive anuria. Cabot and Iber¹ define obstructive anuria as that due to obstruction of the passage of secreted urine, and nonobstructive anuria as that caused by parenchymal pathologic changes that interfere with secretion. For a more specific group, nonobstructive anuria may in turn be divided into anuria due to true parenchymal disease of the kidney and that due to extrarenal factors unassociated with the kidney itself. The following classification outlines the conditions most frequently encountered in urinary suppression.

- Obstructive anuria
 - A. Obstruction of vesical neck (carcinoma, calculi and prostatic hypertrophy)
 - B. Ureteral and renal obstruction (calculi, inflammatory strictures, crystals of sulfonamide drugs, intrinsic carcinoma of the urinary tract, extrinsic carcinoma of the pelvic organs and abdominal tumors, trauma and misplaced sutures)
- Nonobstructive anuria
 - A. Extrarenal disease (cardiac decompensation, intestinal obstruction, peritonitis, gastrointestinal hemorrhage, medical and surgical shock), dehydration and burns
 - B. Renal disease
 - 1. Primary parenchymal lesions (glomerular nephritis, pyelonephritis, nephrosclerosis, polycystic kidneys, toxemia of pregnancy, lipid nephrosis and amyloid disease)
 - 2. Poisons (mercury, lead, cantharides, phosphorus, turpentine and oxalic acid)
 - 3. Nephrotoxic agents (acid hematin deposition after transfusions, black-water fever, myohematin deposition after crushing injuries and tubular deposition of sulfonamide crystals)
 - 4. Hepatorenal syndrome
 - 5. Cortical necrosis
 - 6. Thrombosis of renal artery or embolism

DIFFERENTIAL DIAGNOSIS

A careful history-taking saves time otherwise spent in observation and unnecessary studies. This is particularly true in cases of obstructive anuria, usually preceded or accompanied by pain in the bladder, abdomen or regions of the kidney that points to the source of anuria. The significance of a history of stones, operations or infections associated with the genitourinary tract or of treatment of carcinoma of the cervix or bladder should be kept in mind. A history of drug consumption is easily overlooked. In cases that have been followed or are under treatment the etiology is usually easily ascertained, whereas in patients who present themselves in anuria, the history may be the only lead that one obtains.

Physical examination in many cases helps to supply the explanation. In the obstructive anurias the most frequently found abnormalities are prostatic disease in men and pelvic disease, such as carcinoma of the cervix or pelvic tumor, in women. Occasionally an abdominal tumor or enlarged tender kidneys are present.

Many of the nonobstructive anurias are quickly ruled in or out by physical examination. Vascular collapse due to loss of blood, coronary thrombosis, dehydration and diabetic coma are usually brought to light by examination. Emboli lodging in the renal artery usually originate in the heart, where mural thromboses are formed owing to myocardial infarction, rheumatic heart disease or bacterial endocarditis, with or without ventricular fibrillation. The hepatorenal syndrome may develop without jaundice, but usually jaundice is present. In any patient who presents jaundice and anuria, this syndrome ought to be kept in mind. Cortical necrosis is most commonly found following pregnancy or as a result of trauma, although it has been known to occur after a minor operation. Electrolyte imbalance (retention or depletion of sodium chloride) may show itself in either edema or dehydration, but the imbalance is secondary to some other disease such as nephritis in retention or gastrointestinal disease with vomiting in depletion. The findings in

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primary renal disease are well known and need no comment here.

Diagnosis may depend on accessory data. A plain abdominal x-ray film should always be made in obscure cases of anuria. Unsuspected calculi and abdominal or renal tumors may give the clue to the diagnosis. Occasionally an intravenous pyelogram gives valuable information at the onset of urinary suppression; it may be obtained with safety if the nonprotein nitrogen is not over 60 mg. per 100 cc. In general, intravenous pyelograms give little information when the nitrogen retention is above this figure. If the diagnosis is in doubt, one should not hesitate to obtain cystoscopic examination and retrograde pyelograms with Diodrast, Skioldan or Hippurin. Sodium iodide as a retrograde dye should not be used, since it is irritating. The risk of a skillfully performed procedure is slight when balanced against the precise information that one obtains. The need for retrograde pyelography is exemplified by the difficulty one may have in differentiating ureteral obstruction due to sulfonamides from tubular obstruction due to transfusion reactions occurring in a case under sulfanamide therapy.

The laboratory data of particular value are the composition of the urine, the levels of nonprotein nitrogen, protein, chloride, sodium and sugar in the serum or blood and the carbon dioxide combining power or content of the plasma. The most impressive finding in the urine is of course gross hematuria, but it is usually present when the diagnosis of the underlying disease is relatively simple—for example, tumors encroaching on and eroding the mucous membrane of the genitourinary tract or the presence of kidney stones. Hematuria is ordinarily absent preceding extrarenal anuria, although initial hemoglobinuria is sometimes seen. Primary parenchymal renal disease rarely exhibits gross hematuria. This is true also of poisons and nephrotoxic agents, where anuria is frequently preceded by hemoglobinuria and cortical necrosis. In 117 cases of renal infarction reported by Hoxie and Coggin² gross hematuria occurred in only 4 (3 per cent), whereas microscopic hematuria was observed in 35 (30 per cent). The value of white cells and casts in the absence of dehydration and of red cells at any time are evident. A nonprotein nitrogen level in excess of 40 mg. per 100 cc. is considered elevated and warrants a search for the etiology. Serum protein levels below 5 mg. are often accompanied by edema, sometimes associated with edema of the kidney, albuminuria and decreased kidney function. Sodium and chloride are lost in considerable amount in vomiting and result in dehydration (see discussion of Case 3). Retention of sodium chloride, as in primary renal disease, may further increase edema by causing retention of fluids. A sodium chloride level in whole blood exceeding or lower than 450 to 500 mg. bears consideration, in both the etiology and the treatment of renal failure.³ Anuria may be

present in diabetic acidosis when the carbon dioxide plasma content falls below 20 vol. per cent. Hyperglycemia without acidosis, except experimentally and in the rare cases in which intravenous glucose is indiscriminately administered in large amounts, does not cause anuria.

TREATMENT

Obstructive anurias are usually due to vesical or ureteral blockage. In obstruction of the vesical neck the processes are usually of long standing, and in such cases gradual decompression is desirable. During the preliminary decompression the general condition may be improved by transfusions and intravenous salt solutions, so that if operative procedures are later necessary they can be carried out with less risk. When ureteral obstruction is present catheterization of the ureters may relieve the obstruction. At times ureterostomy or nephrostomy is necessary as a temporary procedure to relieve obstruction and to allow the return of renal function. When conditions permit, removal or correction of the primary cause of obstruction may be done, as in ureteral blockage from carcinoma of the bladder. In general, even dangerously ill patients stand necessary procedures on the kidneys or ureter for relief of obstruction remarkably well, and improvement begins quickly with the onset of diuresis. It is not unusual for patients with a high nonprotein nitrogen (200 to 300 mg. per 100 cc.) and generalized edema to recover rapidly if the obstruction is acute and little chronic renal disease exists.

Postoperative care is principally a matter of the proper administration of fluids, guided in particular by frequent determinations of the nonprotein nitrogen and chloride. Occasionally peripheral vascular collapse occurs, following a genitourinary operation. At times this condition is puzzling and persistent and in spite of plasma or transfusions lasts for several days. In such cases active measures to combat shock must be unremitting, for if shock is long continued, degenerative tubular disease of the kidneys may result. A lowered serum protein level and anemia should be corrected by transfusions of whole blood or plasma. Low blood chloride level should be corrected by the giving of intravenous normal or hypertonic salt solution.

A frequent mistake in therapy is the aimless administration of intravenous fluid. Dehydration should be corrected rapidly, but fluid should not be given to the point of producing edema. The administration of fluids should be governed by the rate of renal excretion and by the level of the nonprotein nitrogen and chloride. If the chloride is normal in the presence of dehydration a 5 per cent dextrose solution in distilled water should be used. If excess fluid is given in the absence of renal excretion in older patients, the circulation may be embarrassed and may further interfere with restoration of renal function.

The nonobstructive anurias are more frequent than the obstructive. Of 78 cases collected by Ot and Iber¹ only 29 were due to obstruction of any outflow. In extrarenal anuria, the present complaint is usually not lack of urine but a group of symptoms that point to some other underlying cause, although Segal and Read² reported 2 cases of gastrointestinal perforation without symptoms other than anuria. In these cases the anuria served to obscure the true condition. Hemorrhage in the gastrointestinal tract, cardiac failure, uremic coma and dehydration from nausea, vomiting or diarrhea, however, are usually fairly obvious. An occasional development of severe oliguria or anuria in such cases may complicate the clinical picture, and certainly makes treatment more difficult.⁴ This secondary nitrogenous retention is so rare in some cases as to be the actual cause of the anuria.

In primary renal disease treatment produces less dramatic results. The various measures used to promote diuresis are well known. The administration of diuretics, together with a salt-free diet, and the giving of limited fluids in the presence of edema usually constitute the treatment. The most frequently encountered renal poison is bichloride of mercury. Early administration of sodium formaldehyde sulfoxalate may be helpful; otherwise supportive treatment is necessary. The early peripheral collapse seen in these patients may be prevented by the giving of intravenous salt solution, glucose solution or plasma. Usually within forty-eight hours there is nitrogen retention, sometimes associated with lowered chloride and diminished alkali reserve. Talbott and his associates⁵ suggest the use of alkali, since the effectiveness of sulfoxalate is thus enhanced and since the alkali reserve is partly depleted.

Nephrotoxic agents are not infrequently seen in hospital practice,⁶ where transfusions and sulfonamides are so widely employed. When hemolysis occurs as the result of transfusion reactions, acid uric acid is precipitated in the kidney tubules. Many workers advise the preliminary administration of sodium bicarbonate by mouth to assure an alkaline urine for prevention of this precipitation when hemolysis occurs. This is especially valuable when difficulty has been encountered in obtaining a perfect cross matching prior to transfusion. After such an accident occurs, the early administration of intravenous sodium bicarbonate or lactate may be lifesaving. Once precipitation occurs, little can be done. Even then, however, it is worth while to administer intravenous salt solution or sodium lactate to keep the uninvolved tubules functioning. As a rule the sulfonamides are crystallized in the pelvises of the kidneys or in the ureters as well as in the tubules. In such cases catheterization and lavage of the ureters and pelvis are extremely satisfactory in dislodging the loosely conglomerated

crystalline deposits. The sulfonamides may cause hemolysis and produce the same train of events as that seen in hemolysis from transfusion reactions. During the present war occasional cases of kidney tubular obstruction have been seen following crushing injuries. This may be due to the deposition of myohemoglobin formed in the crushed muscles. It has been suggested that the tubular damage in these cases is of a chemical nature, and that the danger of renal failure in patients subjected to crushing injuries should be anticipated and prevented. The application of a tourniquet to the injured limb and re-establishment of circulation have been advised as soon as measures were taken to produce diuresis. Measures to prevent tissue breakdown, such as packing the extremity temporarily in ice, may be helpful. Alkalinization is suggested.⁷

The hepatorenal syndrome is still a poorly understood phenomenon. Nitrogen retention and even anuria are occasionally found in patients with liver disease, with or without jaundice. This syndrome should therefore be anticipated and thus prevented in cases with gall-bladder disease and primary liver disease.⁸ Every patient presenting himself for gall-bladder surgery should have a critical appraisal of renal function. Prevention of nitrogen retention may be managed by adequate fluids, if not by mouth then intravenously. The carbohydrate intake should not fall below 150 gm. in twenty-four hours.

Cortical necrosis of the kidneys is occasionally seen post partum and following severe — usually abdominal — trauma.^{9, 10} Previous writers have said that the disease is always fatal.

Thrombosis of the renal arteries with renal infarction is occasionally seen as the result of emboli from the left side of the heart. There is little to do when this occurs save to support the patient generally and to prevent shock.

Decapsulation has been advised for anuria due to transfusion reactions and in particular to bichloride poisoning. Talbott⁶ mentioned a case that one of us (W. F. L.) had an opportunity to follow and that gave evidence of the futility of decapsulation in restoring renal function after such reactions. On the fourth day of anuria the ureters were catheterized and the right kidney was decapsulated. A flow of urine began twenty-four hours after operation. No difference in urine volume was shown between the two kidneys. Six weeks later, when a normal urine volume and nonprotein nitrogen level were present, clearance tests with inulin and Diodrast were done with catheters in each kidney. There was no notable difference in function between the kidneys.

Several cases of urinary suppression have been encountered that illustrate points of interest in the management of anuria. Reports of these cases follow.

CASE 1. Anuria due to postoperative degenerative tubular changes. A 71-year-old man was admitted to the hospital with acute retention of urine that had been present for a few days. Prior to admission catheterization had been done and a large amount of urine withdrawn.

At physical examination the blood pressure was 150/70. The heart and lungs were normal. A right indirect inguinal hernia was present. A markedly enlarged (Grade 3), smooth, elastic prostate was present. There was penile hypospadias.

The patient was catheterized, and the small amount of urine present in the bladder was withdrawn. The urine showed a specific gravity of 1.023, a slight trace of albumin and no sugar. The sediment contained scattered white and red cells but no casts. The nonprotein nitrogen was 35 mg. per 100 cc. The hemoglobin was 93 per cent (Sahli), the red-cell count 4,940,000, and the white-cell count 17,000.

Cystoscopic examination revealed a markedly trabeculated bladder and large lateral prostatic lobes. Since the patient's general condition was excellent, and since it was thought that no improvement could be expected from continued catheter drainage, a perineal prostatectomy was done. Immediately after operation the patient's condition was good, but a few hours later a severe hemorrhage into the bladder occurred. Since the perineal bag and the urethral catheter could not be irrigated, a suprapubic cystostomy was done under local anesthesia, bleeding being controlled by a Hagner bag. The blood pressure fell to 60/40. Two transfusions of 500 cc. each were given, and the blood pressure gradually rose to 110/60 during the next 24 hours. On the 1st postoperative day, however, the blood pressure ranged from 80/40 to 90/60 despite the intravenous administration of glucose solution, normal saline solution and stimulants. For the next 4 days the systolic pressure remained below 120, and during the 5 days after operation there was practically no urinary secretion. The nonprotein nitrogen rose to 153 mg. on the 3rd postoperative day. During this time 14,000 cc. of 5 or 10 per cent glucose in normal saline solution or distilled water was given intravenously, and on one occasion 50 cc. of 50 per cent glucose was given without effect. Edema appeared. The hemoglobin dropped to 58 per cent, and the serum protein to 4.8 mg. per 100 cc. The urinary secretion was 900 cc. on the 5th postoperative day and between 1000 and 3100 cc. during the following week. Despite this apparent improvement the nonprotein nitrogen rose to 245 mg. On the 12th postoperative day the patient developed bronchopneumonia. Oliguria developed and was followed by coma, and death occurred on the 17th postoperative day. The carbon dioxide content of the plasma at one time reached 32 vol. per cent but did not go below this figure. The sodium chloride level remained within normal limits.

Post-mortem examination showed pneumonia of the left lower lobe, healing ischemic necrosis of the liver and acute tubular degeneration of the kidneys. There was marked dilatation of the kidney tubules, with some areas showing regeneration.

This patient stood the operation well. The serious secondary hemorrhage with prolonged shock seemed to be the cause of the renal failure. The blood pressure was below or barely at the secretory level for about twenty-four hours. One can assume on the basis of the microscopic study of the kidneys that there was no appreciable chronic renal disease and that therefore the anuria resulted from the continued low blood pressure, acute degenerative changes associated with ischemia, an acid-base disturbance of the blood or a transfusion reaction. On the basis of blood chemical findings an acid-base disturbance can be excluded. For a time the possibility of transfusion kidneys was considered, but this was ruled out by autopsy. It is concluded that an acute degenerative process of the tubular epithelium associated with or due to poor circulation resulting from continued low blood pressure was the mechanism that prevented prompt recovery of

kidney function after the initial anuria. Some chronic back-pressure changes may have played a part. The low specific gravity of the urine after operation tends to support the assumption that the tubules concentrated poorly. Death resulted from terminal pneumonia and circulatory failure, since kidney function was improving even after death seemed inevitable. The chief point of interest in the case is the cause of tubular degeneration.

How could this case have been treated better? Of course, the obvious answer in such cases is to prevent, or at least to recognize and arrest, hemorrhage before serious shock develops. Occasionally, as in this case, the bleeding is so sudden and profuse that much blood is lost in the bladder before it can be recognized and treatment instituted. The blood loss was extreme, because even after two transfusions the hemoglobin was only 58 per cent. More transfusions shortly after the first two or, still better, the administration of plasma instead of intravenous fluids might have prevented continued shock and kidney damage.

CASE 2. Anuria due to ureteral stones and a solitary kidney. A 52-year-old woman had a left nephrectomy performed by one of us (W. F. L.) in December, 1940, necessitated by a calculous pyonephrosis. An intravenous pyelogram showed a normally functioning and appearing right kidney. The right ureter was not catheterized for fear of introducing infection. Owing to the patient's poor general condition the left ureter, which contained a large stone, was not removed. Because of persistent infection in the urine and pain in the left lower quadrant of the abdomen, the left ureter was removed in March, 1941. Up to that time the patient had had no symptoms referable to the right kidney. Following the ureterectomy she was given a course of sulfathiazole therapy. The urine became clear. She remained well until June 13, 1940, when she was seized with sudden, sharp pain in the left upper quadrant of the abdomen and the flank. This was followed by chills, fever, nausea and vomiting.

On admission to the hospital the temperature was 105°F., the pulse 124, and the respirations 28. There was generalized edema. The patient was irrational and obviously very ill. The lungs were clear. The heart sounds were rapid and weak but otherwise normal. The blood pressure varied between 75/40 and 50/25. The abdomen was distended, and muscle spasm and tenderness were present in the right upper quadrant and the flank. The kidney could not be palpated.

No urine was present in the bladder. The hemoglobin was 76 per cent, the red-cell count 4,030,000, and the white-cell count 12,700. The nonprotein nitrogen was 65 mg. per 100 cc., and the blood chloride level was 507 mg. per 100 cc. A plain abdominal x-ray film was relatively unsatisfactory owing to gas-filled intestines, but no calculi were visible.

It was obvious that the cause of anuria must be determined quickly, and accordingly a cystoscopy was done on the day of admission. A catheter passed quite easily to the level of the right kidney, but no urinary drainage took place. It was possible to inject 10 cc. of fluid through the catheter and to recover most of it, so that it was assumed that the eye of the catheter rested in the renal pelvis. The catheter was left in place during the night. Five per cent glucose solution was given intravenously and caffeine with sodium benzoate was used. The blood pressure remained at 60/40, and no urine was obtained by ureteral catheter or from the bladder.

The next day there was no improvement in the general condition. The nonprotein nitrogen was 92 mg. per 100 cc., the blood chloride 531 mg., and the carbon dioxide content of the plasma 40 vol. per cent. The cause of anuria was puzzling, but it was necessary to assume an obstruction, unless an unusual situation, such as cortical necrosis or occlusion of the renal artery and renal infarct, had occurred.

loration of the kidney was therefore carried out under ether, oxygen and ether anesthesia. When the upper ureter was exposed, a group of small stones were palpated easily removed. The ureter below this level was exposed and found to be patent. A large catheter slipped into the renal pelvis, but no urine was obtained. The ureterostomy was well. A trans-renal injection

200 cc. of a 5 per cent glucose in saline solution. The state of shock persisted. No urine was secreted. Two centimeters of adrenocortical extract was given every 4 hours. The blood pressure quickly rose to 110/60 and urine was secreted. The adrenocortical extract was continued for 36 hours, during which time the blood pressure rose to 160/100, where it remained for several days, returning to the normal level of 135/80. Following the onset of urinary secretion 540 cc. was passed in the first 24 hours, 1800, 3300 and 3900 cc. on successive days. The non-protein nitrogen was normal 1 week after operation. Follow-up examination showed some hydronephrosis but no calculi. The ureterostomy catheter was removed on the

shock. In this case a preoperative diagnosis of calculi blocking the ureter was not made, but it could have easily been made with a pyeloureterogram. It was thought that the ureteral catheter had passed to the kidney pelvis and that therefore the cause of anuria was not obstruction. Exploration of the kidney seemed the only course and was fortunately successful. Although the patient's condition was poor, operation affected her but little. The continued state of shock was the obvious cause of anuria once the obstruction had been relieved. The usual methods for treatment of shock were of no avail. In this case adrenocortical extract used empirically seemed lifesaving, although one wonders what the course would have been if it had not been used. It should be noted that hypertension

TABLE 1. Summary of Data in Case 3.

Post-operative day	CLINICAL COURSE	PARAFORMALIN INTAKE cc	OUT PUT cc	BLOOD SUGAR mg/100cc	BLOOD N P N mg/100cc	PLASMA CARBON DIOXIDE vol %	HEMO GLOBIN gm/100cc	INSULIN units	URINE
1	Blood pressure 90/70, spinal fluid normal	1500 (saline by clysis)	0	342	95	50	16.2	10 (cryst) 20 (prot)	S g 1.017; v s t albumin; no sugar, many white cells and 1-3 red cells
1	Blood pressure 140/80, patient semicomatose.	1500 (saline by clysis) 1000 (5% glucose i v)	10 (catheter)	317 263	108	—	—	10 (cryst) 20 (prot)	No sugar, no casts, 8-10 white cells and 10-15 red cells
2	Patient drowsy	3000 (2.5% glucose i v)	850	400	110	—	—	40 (cryst) 20 (prot)	No sugar
3	Patient improved and less drowsy	2000 (2.5% glucose by clysis) (postoperatively)	1950	—	—	—	—	10 (cryst) 20 (prot)	No sugar
4	Patient improved, food taken	2000 (2.5% glucose by clysis)	1900	183	70	—	—	6 (cryst) 20 (prot)	No sugar
5	Patient greatly improved	2000 (2.5% glucose by clysis)	1300	—	—	—	—	20 (prot)	No sugar
6	Patient rational and eating well	0	1100	154	—	—	—	20 (prot)	No sugar
7		0	800	—	—	—	12.2	16 (prot)	T of albumin, no sugar, 8-10 white cells, no red cells or casts
10		0	—	140	28	—	—	12 (prot)	Phenolsulfonephthalein excretion 24% in 15 min and 40% in 2 hr
14		0	—	—	—	—	—	12 (prot)	
15		0	—	143	28	—	—	12 (prot)	

5th postoperative day, and the wound was healed by the 1st day. The patient was discharged 23 days after operation and has since remained well.

There are several interesting points brought up by this case. What was the cause of the shock that made the case so difficult to treat? We do not recall a case of a blocked ureter by stone when the kidney involved was solitary or when the opposite kidney was normal with associated shock. In fact, one would suppose that a compensatory mechanism would produce hypertension. In a recent case similar to the one reported above in which anuria resulted from blockage of a solitary kidney by a stone at the ureteropelvic juncture, a compensatory hypertension was noted that disappeared when the stone was removed.

The cause of shock may have been pain, although in this case it was apparently not so severe as to cause shock. Toxemia from an acute infection may have been the cause, but a similar infection involving one or two kidneys would not likely result in

persisted for some days thereafter. After diuresis was well established, sulfathiazole in small doses was given, with prompt disappearance of the fever.

CASE 3. *Anuria due to extrarenal azotemia.* A 59-year-old woman had had diabetes mellitus for 9 years. Eight months prior to admission she had a small cerebral thrombosis, from which she recovered without noticeable residual. Following recovery she remained relatively well. The urine had been practically free of sugar on a diet without insulin.

During the 5 weeks before admission the patient felt generally weak and found it necessary to spend much of the time in bed. During this period she felt unable to do much for herself at home and received little care. She grew weaker, but had no definite symptoms until 5 days before admission, when she began to vomit. She did so four or five times a day, and as a result was able to take little fluid or food. She became sleepy and a little short of breath. There was some dizziness. The day before admission she developed weakness of the left arm and leg.

On admission the patient could scarcely be aroused. The blood pressure was 90/70, the temperature 98°F., the pulse 120, and the respirations 28. The skin was loose and dry. The pupils were slightly irregular and myotic. The mucous membranes were dry. The nose and throat were clear, and the thyroid gland was normal. The heart was not enlarged; the rate was regular and no murmurs were heard. Numerous moist rales were heard throughout both lung fields. The

abdomen was soft, and no masses were felt. Arteriosclerosis of moderate degree was present. The left arm and left leg were flaccid, and clonus was present in the left arm.

The blood sugar level, the carbon dioxide combining power and the nonprotein nitrogen were tested and when the results were reported half an hour later the patient was given 10 units of crystalline insulin and 20 units of protamine insulin. A lumbar puncture showed the spinal fluid to be normal. The patient gradually recovered consciousness and continued to improve with the parenteral administration of normal saline solution, followed later by glucose solution (Table 1). The paralysis improved slightly. She was discharged from the hospital with no apparent residual except the paralysis.

The extreme dehydration, initiated by inadequate care at home and perpetuated later by nausea and vomiting, almost resulted in death. This case represents one of the most satisfactory of the extrarenal azotemia group. Although figures on the levels of sodium and chlorides are not available, it is certain

primary requisite in the treatment of such a case as this is the administration of saline solution. Glucose solution should be employed only when adequate replenishment of sodium and chlorides has occurred.

CASE 4. *Anuria due to extrarenal azotemia in the presence of chronic nephritis.* A 66-year-old woman was admitted to the hospital on February 3, 1941, in a comatose state. She was markedly dehydrated. One year prior to admission she had begun to have anorexia and loose, bloody, mucus-containing stools four or five times a day. She had lost about 25 pounds in weight. Six weeks prior to admission she was found to have a polyp of the sigmoid and was referred to the hospital for operation. During the 3 or 4 days prior to admission she had had a good deal of vomiting and had grown progressively weak.

On admission the blood pressure was 120/70. The eye-grounds were normal. Bilateral basal rales were heard in both lung fields. The heart was normal in size, but a harsh systolic murmur was heard over the entire precordium. A

TABLE 2. Summary of Data in Case 4.

HOSP. DAY	CLINICAL COURSE	INTAKE	OUTPUT	BLOOD N.P.N.	P.S.P. EXCRETION	BLOOD CHLORIDE	PLASMA CARBON DIOXIDE	URINE
		cc.	cc.	mg./100cc.	%	mg./100cc.	vol. %	
1	Blood pressure 120/70; basal rales; patient comatose and dehydrated.	2000	300	—	—	—	—	Albumin 40 mg.; 4-5 red cells.
	Patient's condition unchanged	4200	2400	239	Tr. (1/4 hr.) 25 (2 hr.)	—	—	
2	Blood pressure 120/70; basal rales; fluids by mouth; patient lethargic but not dehydrated.	4200	1800	195	—	342	37	
3	Patient semilethargic but slightly improved	4000	1500	188	—	384	43	
4	Patient improved	4500	1800	135	5 (1/4 hr.) 27 (2 hr.)	460	—	Albumin 50 mg.; many red and white cells.
5	Patient rational and much improved; pyelograms normal.	6000	2400	102	—	560	—	
6	Continued improvement	6000	2400	—	—	—	—	
7	Temp 100°F. (? infection of urinary tract following pyelography)	3900	600	63	Tr. (1/4 hr.) 2 (2 hr.)	597	—	Many white cells
8	Chill and temp. 102°F. (? urinary infection); sulfathiazole (4 3 gm.).	4000	600	63	—	540	—	
9	Patient lethargic; ureters catheterized (no obstruction); sulfathiazole (6 gm.).	4200	300	66	—	516	—	Sulfathiazole crystals and red cells
10	Sulfathiazole (1 gm.)	4000	0	85	—	—	—	
11	Coma and death		0	—	—	—	—	

that with five days of vomiting reduction in these electrolytes occurred. As Gamble¹¹⁻¹³ has shown, the electrolytes largely determine the volume of body fluids, and dehydration is a secondary phenomenon in an adjustment process whereby the osmotic pressure of the extracellular and intracellular fluids is kept in proper relation. The chlorides can be replaced in part by bicarbonate, but no source of intrinsic sodium is available and this substance must be replaced, when lost, from an extrinsic source. Ginsburg¹⁴ showed in his case that administration of fluids is not enough to ensure recovery. In fact, the administration of isotonic glucose solution alone may do harm through the production of a so-called "electrolytic vacuum" into which diffusion of sodium and chloride occurs, with further depletion of the body store. The nitrogen retention in such cases is secondary to peripheral circulatory failure, with reduction in effective glomerular filtration. The nonprotein nitrogen may be further increased by protein catabolism associated with starvation. It thus appears that the

tentative diagnosis of extrarenal azotemia was made. With the degree of dehydration as a result of diarrhea it was difficult to determine how much renal damage was present. Saline solution and 5 per cent glucose solution were repeatedly given intravenously. For the first 48 hours the patient's condition was unchanged, but thereafter she began to improve and continued to do so. Large amounts of mucus were passed by rectum, but despite the fact that the amount passed sometimes exceeded 1000 cc., it was possible to maintain an adequate degree of hydration.

Table 2 illustrates the changes that occurred in the urinary output, the nonprotein nitrogen, the phenolsulfonephthalein excretion, the serum chloride, the plasma carbon dioxide and the urine. Concomitant with the fall in nonprotein nitrogen, the hemoglobin level and the red-cell count also fell from 126 per cent and 6,670,000, respectively, on admission to 96 per cent and 4,640,000 on the 7th hospital day, when the nonprotein nitrogen reached its lowest level (63 mg. per 100 cc.).

On the 5th hospital day the patient was rational. She seemed strong and was able to take some fluid and food by mouth. It was thought at that time that she would continue to improve and that eventually she might be prepared for operation. However, the stationary phenolsulfonephthalein excretion and the drop in urinary output to 600 cc. were not taken into full account.

On the 7th day the patient had a slight fever, and on the following day she had a shaking chill. The latter was thought to be due to a urinary infection and she was given sulfathiazole. She received 11.3 gm. (170 gr.) in the ensuing

ours, but failed to improve. Oliguria became severe, the ureters were catheterized to be certain that no action was present as a result of chemotherapy. The patient lapsed into coma shortly thereafter, became anuric, died on the 11th day.

It was thought that sulfathiazole therapy might have had something to do with the secondary oliguria, but actually output decreased and the nonprotein nitrogen became anuria prior to the institution of sulfathiazole therapy.

Autopsy a large, fungating carcinoma of the rectosigmoid, measuring 12 cm. in diameter, was found. The cysts of the kidneys were granular and marked by numerous small, clear cysts. A number of shallow scars were present on each kidney surface. The aorta showed marked atherosclerosis, particularly in the abdominal portion. On microscopic examination cholesterol deposits were found in coronary arteries. The glomeruli of the kidneys showed considerable variation in size, and many were scarred and necrotic, a few being completely obliterated. There were no areas where recent tubular degeneration had occurred.

This case illustrates the great changes that may occur in a patient with pre-existing renal disease when an extrarenal factor is superimposed. The patient may well have lived for some time had the ureters, which were already damaged, not had this as a burden to combat. This case affords a contrast to Case 3, in which the kidney function returned to normal and in which no chronic kidney disease was apparent.

Case 5. Anuria due to chronic glomerulonephritis. A 62-year-old woman had had diabetes mellitus for 6 years. She was first seen in 1939 when she had slight dyspnea on exertion, occasional cough. On physical examination the blood pressure was 170/80 and the weight 170 pounds. The heart was enlarged to the anterior axillary line and a loud apical systolic murmur was heard. The lung fields were clear. Edema was present. The nonprotein nitrogen was 23 mg. per 100 cc. The urine showed a specific gravity of 1.007, a slight trace of albumin and no sugar. The sediment contained 2 to 3 white cells per high-power field. A phenolphthalein test showed excretions of 6, 12 and 33 cc. in $\frac{1}{2}$, 1 and 2 hours, respectively.

The patient was next seen on June 28, 1940, complaining of gradual loss of vision in the preceding 6 months. She was unable to read. The pupils were too small to permit ophthalmoscopic examination. The urine showed a specific gravity of 1.010 and 100 mg. of albumin. The sediment contained 8 to 10 hyaline casts or finely granular casts per high-power field, no blood and many white cells, both single and clumped.

The patient was next seen in March, 1941, when following severe cold 2 weeks previously she was found by her physician to have albuminuria. She began vomiting occasionally and noticed some swelling of the feet. Oliguria had been present several weeks before admission. At admission on March 22, the blood pressure was 172/92. The heart was enlarged to the left anterior axillary line, the rhythm was regular, and a systolic murmur was heard. There was no edema of the sacrum and of the lower extremities.

The urine showed a specific gravity of 1.020, a trace of albumin and a normal reaction, with a sediment showing no casts, rare red blood cells and many white cells per high-power field. Later many white cells were found. The nonprotein nitrogen was 125 mg. per 100 cc. The patient was given 5 per cent glucose solution intravenously on several occasions. The urinary volume was normal, however, and the largest volume during a 24-hour period in 2 weeks' time was 300 cc., with a daily average of 100 cc. The nonprotein nitrogen gradually increased from 125 to 180 mg. over a period of 10 days in the hospital. Despite this, she remained fairly comfortable and capable up to the last 5 days of her illness. For the last 24 hours of her hospital course she was completely anuric.

Additional chemical data showed the serum protein to be 5.2 g., the albumin-globulin ratio 0.68, and the blood chloride 96 mg. per 100 cc.

Autopsy showed chronic glomerular nephritis.

This case illustrates the relatively slow onset of symptoms from urinary suppression in patients with chronic nephritis. Although for a period of two weeks this patient had increasing suppression of urine, she did not feel sick enough to visit the hospital until this period of time had passed. This case is in contradistinction to the obstruction anurias, in which the course is stormy practically from the outset. The duration of life after the onset of anuria in cases of nephritis is usually less than a week. This is shorter than the duration of life after obstruction occurs, which is apparently due to the changes that have already taken place before stoppage of urine occurs. Kutzmann¹⁵ stresses the relative comfort of patients with primary renal disease.

Case 6. Anuria associated with obstructive jaundice. A 67-year-old woman first noted gas on the stomach in the evening, relieved by eructation, several months prior to admission. Shortly thereafter she developed cramps in the right upper quadrant of the abdomen lasting for 12 hours and followed the next day by chills, a temperature of 103°F. and clay-colored bowel movements. She entered the hospital with jaundice. The extent of jaundice was not reported, but she was known to have had clay-colored stools. Oral gall-bladder dye showed a nonfunctioning gall bladder. Within the course of 24 hours after admission suppression of urine gradually developed and the nonprotein nitrogen was found to be 82.5 mg. per 100 cc. The urine was positive for bile, with a slight trace of albumin. The sediment was negative.

The patient was given intravenous normal saline solution and glucose solution intravenously. There were 24 hours during which no urine was passed. The jaundice began to improve spontaneously, and associated with this urine was passed and there was a gradual decrease in the nitrogen retention.

Four days after treatment was started the nonprotein nitrogen had dropped to 60 mg. and 3 weeks later it was 17 mg.

The patient was first seen by us 3 months following this episode, with a complaint not directly related to the above. In the course of therapy, however, an intravenous pyelogram was done. This showed poor renal function on each side. The output of dye was not sufficient for adequate delineation of structures. There was no calcification. A phenolphthalein test showed excretions of 21, 8 and 10 per cent in $\frac{1}{2}$, 1 and 2 hours respectively. The urine had a specific gravity of 1.020, with a slight trace of albumin and no bile. The sediment showed 13 to 14 white cells per high-power field but no red cells or casts. The nonprotein nitrogen was 37 mg. per 100 cc. An electrocardiogram was normal.

This case illustrates the urinary suppression not uncommonly seen in patients who develop jaundice in the presence of pre-existing renal damage. Thompson, Frazier and Ravdin¹⁶ believe that in obstructive jaundice associated with evidence of poor renal function there usually exists a renal lesion that is complicated by cholemic nephrosis. They demonstrated a high incidence of glomerular lesions at autopsy, and these changes predominated in elderly patients. The main lesion associated with the hepatic disorders was dilatation and compression of the lining epithelium, with various secondary changes. These authors emphasize the necessity of care as regards the renal function in such cases, since the latter may be the determining factor in improvement. Bartlett¹⁷ mentions the rarity of nephritis associated with other diseases of the abdominal viscera.

The best treatment is prevention by adequate administration of fluids and early relief of jaundice. Essentially the treatment after oliguria has developed consists in the intravenous administration of glucose, at least 1500 cc. of 5 per cent solution daily, in an attempt to initiate diuresis. The blood sodium chloride level should be followed and kept within the normal limits of 450 to 500 mg. per 100 cc.

SUMMARY

The etiology, diagnosis and treatment of anuria are outlined.

The importance of frequent complete blood chemical determinations and the proper administration of fluids, as to both type and quantity, are emphasized. Excessive fluid by vein in anuria may be harmful, and when fluid is given the quality and quantity should be given consideration.

Six cases are discussed in detail. These illustrate various points in the management of anuria. It seems obvious that in most cases early treatment, in the absence of severe chronic renal disease, should result in recovery.

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DR. SAUL TCHERNICHOVSKY, 1875-1943

A Hebrew Medical Poet Laureate

HARRY A. SAVITZ, M.D.*

BOSTON

A poet alone has the qualifications to represent worthily that which is great and heroic in a people.
— Maurice Maeterlinck.

DR. SAUL TCHERNICHOVSKY was a doctor of medicine by profession and practiced with distinction all through his life, but his fame rests on the fact that he was the uncrowned king of modern Hebrew poetry. For nearly half a century, Bialik and Tchernichovsky were the renowned Hebrew poets. During the last decade, the laurels of the so-called "Hebrew poet laureate" were worn by Dr. Tchernichovsky.

The Hebrew poet laureate holds no official position, nor does he receive even the minimal salary of the British poet laureate, that of a barrel of wine and £120 a year. But his dignity and honor are none the less, and perhaps even more. The Hebrew poet laureate is neither appointed nor elected. But instinctively there is a feeling among his fellowmen that he is "the" poet. Somehow they sense that he is their spokesman; his views express their remote hopes, as well as their present sorrows. It appears as though his pen were dipped in their blood and that he more than any other reveals to the world their innermost woes and pangs, as well as their

aspirations and hopes. His poetry may symbolize the very period they are living in, and speaks the language that is so typically their own. On reading this poetry one experiences the feeling that it is what he himself would have said had he the ability to so express it. "Such a poet was Bialik. He symbolized the Hebrew Renaissance with all its complexities. On the other hand, a poet may in a sense be the reincarnation of a period in the past history of a people and so remind them of their forgotten historical task. He may speak a language to which they are not accustomed, yet the people feel in these poetic creations the echoes and reverberations of their poets and prophets. Such a poet was Dr. Tchernichovsky. So when the great poet laureate of the Jewish people, Chaim Nachman Bialik, died in 1934, the laurel, so to speak, was placed on the head of Dr. Tchernichovsky, and he held it with dignity until his death on October 14, 1943. For in his poetry his people finally found the revival of their national instincts and historic trends. He portrayed to the world their heroic past. They felt about him what Maurice Maeterlinck said of the great Belgian poet, Emile Verhaeren, "A poet alone has the qualifications to represent worthily that which is great and heroic in a people."

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But he was more than a poet whose works were read for mere entertainment. He was his people's physician, so to speak. He tried to give them a new outlook on life and to stimulate and develop their springs of emotion, rather than their intellectual resources. He tried to focus their attention to the

Let us unfold the story of this doctor and poet. Tchernichovsky was born on August 20, 1875, in Russia, in the village of Michailovka on the Ukrainian border. This is a country that is well known for the severity of its winters and its burning summers — a vast country in which there is nothing



SAUL TCHERNICHOVSKY
1875-1913

dream of life and to attune their ears to the multitude of harmonious vibrations in nature. Turning to the early history of his nation, he tried to rouse their ancient instincts for life. He tapped all sources and channels of many peoples and tongues, wherever beauty and life were found. So he recreated in Hebrew the classics of various nations. In so doing he reversed the process, for he brought his skill and ability, a poet for all humani-

mild or temperate, a land where the cold blasts from the Arctic Ocean sweep down over great stretches of land uninterrupted until stopped by some mountain chain. These scenic and atmospheric conditions made an indelible impression on the young poet's mind and mood. They became his inheritance for the rest of his life. As he

He continues to describe how he spun his dreams in the image and model of his native land. For there he met the eternal wanderer — you will never guess his name — why, the Wind! He often carried dark leaden clouds and at times just played wildly in God's open spaces — a frolic in treasures of ice and snow. There he heard the shrieks of the wild eagle.

Such was also his fate, the poet concludes. Like the eagle's call, he was often misunderstood, and like the Wind, he wandered from place to place.

Tchernichovsky's personality and works also reveal dominant hereditary traits. He came of a stock of rugged people, physically strong and intellectually curious. His ancestors participated in Russia's wars and survived various persecutions. His great-grandfather lived long enough to celebrate a second confirmation (Bar Mitzvah), for he lived one hundred and thirteen years. His mother's father, Saul Karp, after whom he was named, was a cultured and widely traveled man. He mastered the French, Italian and Russian languages. He translated Ukrainian folk songs into Hebrew and then sang them in their original melodies. Several members of his family participated in the Caucasian wars. His father was a righteous and observant Jew. His mother was a cultured and sensitive lady. Her sister was one of the first women to matriculate in a Russian university. As a student, she was attracted to the revolutionary movement and was exiled to Siberia. It was this aunt who started to teach Russian to young Saul when he was but five years old. Two years later, his father began to teach him Hebrew through the medium of Russian. It is told that in order to commit the Hebrew alphabet to memory, young Saul made models of the Hebrew letters with dough and baked them. These alphabet cookies were the joy of the young lad. This is extremely symbolic, for during the rest of his life he succeeded in modeling many a literary dessert out of the alphabets and legends of various nations. He was then prepared for the source book of Hebrew literature, — the Bible, — which he mastered in its original tongue, and this became part of his being. He was also introduced to the modern Hebrew writers and poets, such as Mapu, Lebenson, Dolitsky and Manne. At the age of twelve, he wrote his first poem, "Uriah, the Hittite," which he illustrated artistically himself. But nothing was preserved of his juvenilia. He was a profuse reader and he continued to study Russian literature in its original and translated works.

In 1890, Tchernichovsky went to Odessa and entered the Commercial High School. There he came in contact with a group of men of great vitality — men whose culture was universal. They were dreamers, men of vision, who tried to forge a new dawn and a new freedom. They were the early "Lovers of Zion." This circle of friends made a lasting impression on the youthful student. It was

while he was in Odessa that his first Hebrew poem, "Bahalomi" ("In My Dream"), came off the press. It appeared in a Hebrew journal, *Ha-Pisgah*, published in Baltimore, Maryland, in 1893.

In 1896, Tchernichovsky was graduated with distinction from that school. During these years he acquired a working knowledge of the English, German and French languages. He had a rare gift for languages. Not only was he able, in a short time, to read and study their literatures in the original, but he was able to utilize these languages in his poetic creations. Thus in 1897 he began his translation of *Hiawatha* by Longfellow, which he rendered in lasting biblical verse.

To be fully prepared for his career of a physician, he had to study Greek and Latin. Here again, he was riding Pegasus on his way to medical school. For in 1896 he started to translate the poems of Anacreon from Greek into Hebrew.

In 1898, Tchernichovsky's first collection of poems was published in Warsaw. It was called *Hezionoth Umanginoth (Visions and Melodies)*. At first, most of the critics were harsh and severe. They were dazzled by this poetry's newness. Here was an outburst of feeling, an explosion of strength. Here were new visions, new melodies. Words were used in new combinations and new arrangements. Here was no stream of old quotations, but words to portray certain moods. The critics did not at first grasp the meaning. Were not our own critics dazzled when Walt Whitman first appeared on the American scene? Here, too, was a prophet and poet who exulted in the new strength and life of America. These fountains of poetry do not necessarily follow the old patterns. So it is strange at first. Yet one writer immediately saw this poetry's merit. Reuben Brainin (1862–1939) was the leading Hebrew critic, essayist and biographer, as well as a writer of beautiful lucid Hebrew. In his introduction to Tchernichovsky's first edition, he exclaims: "Here is indeed a poet who is treading a new path. His muse does not appear in borrowed clothes — to be sure, its wings are young and tender, but there are no foreign feathers on them."

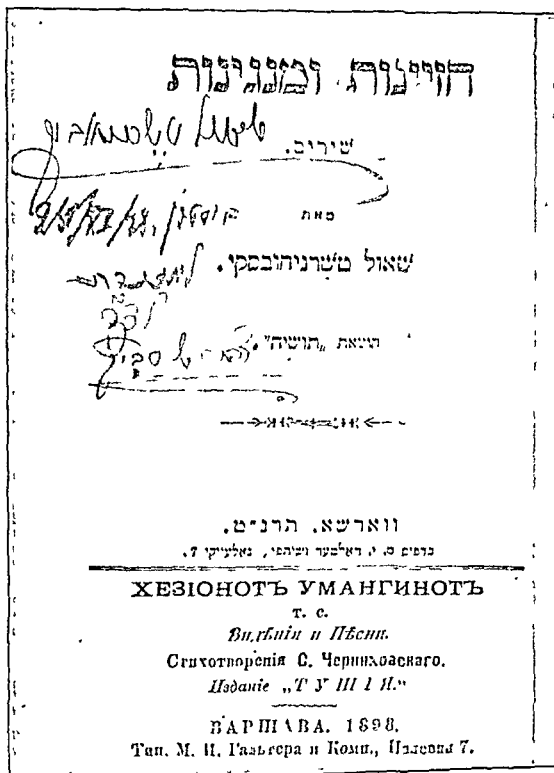
In 1899, Tchernichovsky matriculated in the Medical Department of the University of Heidelberg, and spent four years there until 1903. To broaden his general knowledge, he also studied philosophy for the first two years under Professor Kuno Fischer. He also studied the history of religions. Meanwhile he acquired the knowledge of another language — Italian. Although steeped in medical studies, he never forgot his first love — poetry. This is also true of his entire medical career, which he never abandoned. He may have courted Erato (goddess of lyric and love poetry) for a while and then started to flirt with Calliope, but he never abandoned Minerva. There was no jealousy among the goddesses. On the contrary, as we shall see, his medical study influenced his

poetry, while his poetic sensitivity was revealed in his medical practice. So as a student in Heidelberg he published some of his finest poems, among them "Before the Statue of Apollo," "Baruch of Mayence" and "At the Sea."

The next four years, from 1903 on, we find Tchernichovsky in Lausanne, Switzerland, where

served as assistant in the Royal Institute of Medicine.

During World War I, Tchernichovsky enlisted in the Russian army, serving with distinction from 1915 to 1918. Here the poet of love, life and sunshine became the beloved physician of the ill, wounded and maimed. He saw service in a mili-



An Autographed Title Page of the First Edition of the First Book of Poetry by Tchernichovsky.

received his M.D. degree in 1907. On the completion of his medical studies, he returned to his native land, Russia. For the next three years (1907 to 1910), he served as a physician for the *Zemstvo* (the local town government) in the province of Larkov. There he practiced among the Russian peasants with great success. In 1907, he was arrested in Melitopol, charged with a political offense, but was fortunately released after six weeks of imprisonment. During the next four years he was active in medical work in St. Petersburg, where he

tary hospital and received a medal on discharge, as well as other testimonials, including a Hebrew Bible. Many letters of appreciation by soldiers of the White and Red armies were published in the newspapers. After the war he returned to Petrograd, where he served in another military hospital as assistant director of the Department of Sanitation and Statistics for the Red Cross. When the Bolsheviks came into power, he was sent on a special mission to the Crimea. Up to 1922, he was in Odessa as a physician in various military hos-

That year he went to Berlin, where he lived for several years.

During all these years that Tchernichovsky practiced medicine, he suffered hardships, but his creative activity never ceased. At this time he was engaged in the translation of the *Iliad* and *Odyssey*, as well as in writing many original poems. But not only was he browsing in the world classics: he traveled and visited the lands of many people. In 1925, he visited Palestine and participated in the opening of the Hebrew University on Mount Scopus, where he worked for a short time in the Kupath Holim Hospital, then returning to Berlin. In 1928, he came to the United States. Here he received the honorary degree of Doctor of Hebrew Literature from the Jewish Institute of Religion. In November, 1928, he went to Cambridge, the home of Longfellow whose poems he translated. While here, he visited the Hebrew Teachers College, where American Jewish youths, students at American universities, studied his Hebrew poems. Everywhere in the New World he was greeted as the poet symbolizing the New Palestine and the renaissance of the Hebrew language.

In 1931, Tchernichovsky returned to Palestine, where he became the physician in charge of schools in Tel Aviv. He was also made an honorary citizen of the city. In 1932, forty years after the publication of his first poem, a special Jubilee Committee published his works in ten volumes, which included most of his original efforts, as well as his translations of some of the world's classics. What a luxuriant harvest these ten volumes represent! What a contribution to world literature! Here one finds poetry in practically all its forms — idylls, epics, sonnets, lyrics and dramas, and prose as well. Poetic creations of various peoples and tongues — ancient and modern — attracted his sensitive soul and he rendered them into Hebrew. Songs of ancient Egypt, Babylon and Greece, as well as the works of Shakespeare, Longfellow, Molière, Goethe, Heine, Pushkin and Alfred de Musset, were among his translations. Heroes of these nations were as stimulating to him as some of the Biblical heroes of his own people.

In 1935, as a result of his translations of the Finnish epic *Kalevala*, Tchernichovsky was invited to Helsinki, where he received the award of the Finnish White Rose. Honors were also bestowed on him by the Academy of Athens for his translations of Homer and Plato.

During his stay in Tel Aviv, Tchernichovsky reached the zenith of his productivity. In addition to the continuous flow of his poetical creations, he completed from 1931 to 1933 a Hebrew medical dictionary begun by Dr. Mazia. It is a book of nearly one thousand pages. For each term is given its Latin, English and Hebrew equivalents. Here again, the poet, physician, philologist and scientist found an outlet. Some of the medical terms

have a poetical tinge to them. Where he could not find an old term hidden somewhere in the ancient literature, he coined a new one. Hebrew, by the touch of this doctor-poet's hand, became rejuvenated, young, vivacious, expressing every mood, every flower and every precious stone, as well as many new inventions. In reading his poetry, one feels the vitality, frivolity and energy of a living tongue and at the same time the wisdom and judgment of old age, vast experience and ripened maturity.

In many of his poems, Tchernichovsky endeavored to revitalize his people and to arouse in them a will for the joy of life. He wanted his readers to respond to the symphonic harmonies of nature and to enjoy its sunshine.

For his star is Life, and Life and Love are One,
And death's domain is where there is no sun.

Bialik glorified the *Hamathmid* — the diligent student, the guardian of the holy fire, the intellect. Tchernichovsky, on the other hand, stressed the emotional side, bearing out his philosophy, or rather poetical vision of life, according to which the feelings and emotions are superior to the intellect. A sense of beauty is superior to the accumulation of facts, no matter how essential. As he says:

In all the world, three precious crowns there be,
Each crown with its own light for men to see,
Of strength, of Torah, and of beauty are the three.
Our praise to strength!
To Torah's crown, no less,
Of beauty's worth, who shall attempt to guess?*

In another poem, "*Sholosh Amitoth*" ("Three Truths"), he says:

There are three truths in the world — each truth and its particular glory. The truth of the individual — the truth of strength; the truth of the Torah — the truth of the many — the truth of beauty, the universal truth. Truth of beauty is noble and superior to all.

There is a great deal of truth and realism in these verses. Here is a poetic differential diagnosis of a keen and observant physician. Does not the world witness at the present time the curse of intellect without the slightest sense of beauty? Were not evil forces unleashed on the world by a nation that was technically developed and scientifically informed? Are not the foundations of civilization crumbling because a sense of beauty has given way to technical success?

So the doctor turned to beauty wherever it could be found. This prompted him to say enthusiastically to the statue of Apollo, the symbol of youth, love and life:

To thee I come, O long-abandoned God
Of early moons and unremembered days,
To thee whose reign was in a greener world
Among a race of men divine with youth,
Strong generations of the sons of earth.

For this type of poetical utterance, Tchernichovsky was erroneously labeled as the Greek in Hebrew

*Translated by Dr. M. Waxman.

literature. As a matter of fact, it is the Jew in him that speaks in this way — a Jew conscious of his long literary heritage. Was not the poet of the Song of Songs crying for love and life when he said:

Let him kiss me with the kisses of his mouth —
For thy love is better than wine.

In truth, Tchernichovsky is a firm believer in the God of the Bible, for he ends this poem by saying:

I kneel to life, to beauty and to strength,
I kneel to all the passionate desires
Which they, the dead-in-life, the bloodless ones,
The sick, have stifled in the living God,
The God of wonders of the wilderness,
The God of gods, who took Canaan with storm
Before they bound Him in phylacteries.

Tchernichovsky's rare personality and poetry, the vital elements harmoniously fused and mutually influenced each other. He symbolizes by his person the Jew of the Biblical period, by his nature the Jew of the modern poet and by his training the keen and observant physician. He is neither Hellenistic in his poetry nor pantheistic in his faith. He was sensitive to beauty everywhere. He would use a Greek theme as a frame to reveal more sharply the ideas of his people. This is clearly revealed in the poem "*Ha-Pesel*" ("The Statue"), dedicated to the students of the Hebrew Gymnasium in Lithuania. He colorfully and artistically describes the pomp and ceremony in a Greek temple at the unveiling of a new statue of the God Zeus. The curlew rises and the entire congregation kneels in amazement. Only one person remains standing — the sculptor of this marvelous statue. For at the moment of the unveiling there appears before him the face of the Lord — that is even more sublime, more beautiful and more divine. Does not this poem reveal the great Jew as well as the great poet? When it comes to the suffering of his people, the doctor, as well as the poet and prophet, comes to the aid. Tchernichovsky neither weeps nor mourns. There is nothing pusillanimous about his poetry. He is like a great physician who loses his favorite patient and deeply feels the pain and sympathizes with the family, but calmly analyzes the case and goes to his next patient. Having isolated the cause of the illness, Tchernichovsky is encouraged to conquer the malady and wipe it off the earth. Here is where he differs from his predecessor, the immortal Bialik. During the massacre in Russia in 1909, Bialik wrote a poem called "*Be-ir Ha-Haregah*" ("In the City of Slaughter"). Here he appears as a new Jeremiah, with a modern scroll of lamentation. He proclaims to the world the cruelty of man to man. His descriptions are soul piercing and tear at the fibers of the heart. This poetry conveys the wrath and sorrow that only the poet of a martyred people could describe. It is written in a hammered Biblical style, slow moving and weighty rhythm. The poem gives the effect of a memorial hymn played on a gigantic electric organ whose

vibrations rise to pierce the skies and to shake the earth at the same time. Bialik is at times despondent.

Tchernichovsky, the physician, is more comforting. He speaks in the style of Isaiah. He, too, feels the sorrow, the pangs of injustice, but the doctor is calm and not despondent. In 1920, during the slaughter of his innocent brethren in the Ukraine, he wrote a poem called "*Zoth Thei Nikmatheinu*" ("This Will Be Our Revenge"). "No one listens to the pangs of the widow, no one comforts the infant, but there is revenge in the world." This revenge is not to come by retaliation — he is too sensitive for that. There shall be no retaliation until the image of God is erased from us, as well as the lines of ancient nobility that are on us. It shall not come as long as we bear the yoke of the Ten Commandments. But remember — these acts of murder will poison the very soul and the very fibers of the tormentors. It will breed more cruelty, more immorality and more demoralization. It will penetrate into the heart of the children and their children's children for generations to come. For the cry of blood must be stilled. Here the doctor looks on evil and cruelty as on deadly poisonous bacteria that produce a bacteriophage that eventually destroys the bacteria that produced it. How prophetic is the doctor's prognosis! Nations that permitted evil forces to victimize innocent peoples are now reaping the fruit of the harvest. Here is poetry to be taught to the world, to be included with other rules of medical hygiene for the soul.

Such is briefly the life and work of the doctor and poet, Tchernichovsky. But to appreciate him fully one must read his poems in their entirety and in the original. He belongs to the golden chain of Hebrew poets and physicians. Dr. Tchernichovsky was not a rare phenomenon in the long history of his people. There is a golden tradition of nearly ten centuries of medical Hebrew poets. Each one, more or less, reflected the period of world history in which he lived. As early as the eleventh century, we find the physician in Cordova, Spain — namely, Judah-Ha-Levi (1085-1142). He was a philosopher and a serene and tender poet whose devotional songs in the spirit of the *Psalms* are included in the synagogical liturgy. He too had a longing for Zion that inspired him to compose a number of beloved poems. He too was buried in Palestine in 1142.

During the Golden Age of Hebrew culture in Spain, we find two other Hebrew medical poets: Judah al-Harizi (1170-1230) and Joseph Zabarra (1140-1200). Both were contemporaries of the great Maimonides. All were heirs to a noble tradition of intellectual activity.

In the thirteenth century there lived in Italy the medical Hebrew poet, Immanuel Ha Romi (1265-1330). He reflected the period of his time and was respected by Jews and Gentiles, especially the

literati of the age. He was a friend of Dante and wrote a fine elegy in Italian after the latter's death. In the eighteenth century flourished the poet Ephraim Luzzatto (1729-1792). He died in London. In the nineteenth century there was Judah Lob Katzenelson (born in Tchernigow in 1847; died in Petrograd in 1917). He was a physician and scholar who wrote poems and sonnets, in both Russian and Hebrew, as well as a Hebrew work on talmudic medicine. Finally comes the minor Hebrew poet and physician, Isaac Kaminer (1836-1901).

* * *

Such is the golden tradition of Hebrew medical poets, among whom Dr. Tchernichovsky was the ultramodern. His muse raised him to new heights in poetry.

Tchernichovsky died of leukemia in the Hadassah Hospital in Tel Aviv on October 14, 1943, the first day of Succoth, the holiday of the harvest. His casket was draped in the talith (the prayer shawl) and the Jewish flag. The pallbearers were professors of the Hebrew University and members of the Jewish Agency. The funeral procession was followed by the children of the schools and by soldiers of the Allied forces stationed in Palestine. The poet was buried near his friend, Bialik.

Tchernichovsky is the most modern Hebrew poet who draws his inspirations from the far past —

his roots penetrate deep into the springs that nourished and nurtured the Bible. Like the prophets of old, he also had visions about the future. When his works are rendered by poets into other living tongues, as he rendered the world classics into Hebrew, humanity at large will enjoy its beauty and sunshine, as it does the other sacred writings of his prophets and poets. For Dr. Saul Tchernichovsky had great hopes in the eternal and final victory of man. Mankind may be humiliated at times. "Mobocracy" may unbridle the passions of a populace, and leave the light of civilization a tiny flicker. Yet eventually, our poet believed, the spirit of man will win out.

Laugh, O laugh at all my visions,
For I'm dreaming audibly;
Laugh, for I believe in man still,
For I still believe in thee. . . .
Man shall rise to heights of glory,
Vanity's fetters from him shed,
Till the worker starves no longer,
Spirit freed and hunger fed. . . .
I believe, too, in the future,
Tho' the day's not close at hand;
It will come — then peace and blessing
Will be borne from land to land. . . .
A poet then shall sing a new song.
To beauty exalted then awake;
From my grave, for him, the young one,
They'll pluck flowers, wreaths to make.

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NEW YORK

CHEMOTHERAPY has a long history, progressing from the older treatment of syphilis by mercurial inunctions to the successful use of such agents as arsenicals, bismuth and quinine against syphilis, malaria and other parasitic diseases. No chemotherapeutic agent, however, has affected so many lives so soon after its discovery as have sulfanilamide and the related sulfonamide compounds, which have opened the era of chemotherapy of bacterial diseases. Investigations involving these drugs have not been limited to practical therapeutic problems; they have led to a number of fundamental advances in pharmacology and have had ramifications in related scientific fields. The value and the

limitations of these drugs in overcoming a variety of infectious diseases are widely recognized; this paper will rather be devoted to a review of the broader biologic implications of the knowledge gained in the ten years in which these compounds have been used.

Several attributes of sulfonamide drugs have contributed to the rapid accumulation of knowledge of their pharmacology. These are chemical simplicity and ease of synthesis, which have permitted rapid development of inexpensive manufacture and widespread use; the possibility of synthesis of a wide variety of derivatives of the original sulfanilamide; effectiveness against susceptible organisms without the aid of the body's natural defenses, permitting in vitro study; dissociation as acids; and the possession of a readily diazotized amino group, which permits accurate and simple colorimetric determina-

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tion of concentrations of the drugs at therapeutic levels.

DISTRIBUTION OF THE DRUGS IN THE BODY

The absorption, distribution and excretion of these drugs have been studied extensively, since their concentrations are so readily measured. The bacteriostatic action of a given drug is proportional to its concentration in the body rather than to its dosage. It is therefore desirable so to adjust the dosage as to maintain an optimal concentration in the blood, which strikes the proper balance between effectiveness and toxicity. Blood concentrations of 5 to 15 mg. per 100 cc., which are usually sought for the various drugs, are in general maintained by a daily dosage in adults of 4 to 6 gm. There is, however, significant individual variation in the rates of excretion and of acetylation (which renders the drugs nonbacteriostatic). Patients with decreased renal function excrete these drugs more slowly, so that dosage must be watched even more carefully to avoid excessively high concentrations in the body. Smaller, less toxic doses have been recommended for prophylaxis against the recurrence of rheumatic fever,^{1, 2} and for the treatment of superficial infections of the urinary tract.^{3, 4}

The frequent measurement of blood sulfonamide concentration has shown that therapeutic levels are obtained quickly only with a large initial dose followed by small maintenance doses. Because of the time lag of several hours before an orally administered sulfonamide is absorbed sufficiently to afford a therapeutic blood level, it is advisable in patients with fulminating infections, such as lobar pneumonia and meningitis, to administer the initial dose intravenously in the form of the sodium salt. This system of variable dosage might well be of value with other drugs, since the lack of chemical methods of measuring concentrations of most drugs has caused physicians to think traditionally in terms of fixed dosage rather than according to the more significant concept of concentration in the body. There are wide variations in individual tolerance to certain drugs, such as aspirin and colchicine; methods of measuring blood levels might contribute materially to a rational employment of these substances. This approach has recently been successfully applied to the salicylate treatment of rheumatic fever.⁵

The levels of sulfanilamide found in the cerebrospinal fluid are usually almost as high as those present in the blood, whereas the levels of sulfathiazole are only approximately 25 per cent of the blood levels; the ratios of blood to cerebrospinal fluid for sulfapyridine and sulfadiazine are intermediate. At first this was explained by a supposed poor diffusibility of sulfathiazole through the blood-brain barrier, leading to the conclusion that sulfathiazole, although an excellent drug in the treatment of systemic infections, is a poor choice in the treatment of meningitis. This explanation and

clusion was invalidated by the discovery that the sulfonamides are bound in varying degrees to plasma proteins, particularly to albumin.^{6, 7} Only .20 per cent of sulfanilamide but 75 per cent of sulfathiazole in plasma is bound. The type of binding noted for sulfonamides is a rapidly reversible equilibrium between protein, bound drug and unbound drug. Since only the unbound drug can permeate into the cerebrospinal fluid, it follows that there is no lack of diffusibility on the part of sulfathiazole. Further, since it is highly probable that only the unbound drug is bacteriostatic,⁷ the 1.2 mg. per 100 cc. of sulfathiazole in cerebrospinal fluid, which is essentially protein-free, would be expected to be as effective as the 5 mg. in the corresponding plasma, of which only 1.2 mg. is unbound. This theoretical analysis is supported by numerous clinical observations of the efficacy of the highly bound sulfathiazole and sulfadiazine in the treatment of meningitis. There is now no justification in treating any case of meningitis with the relatively ineffective sulfanilamide. It may also be pointed out that binding to nondiffusible constituents is a mechanism that must be borne in mind in interpreting the distribution of any drugs or other permeable substances between intracellular and extracellular fluids or between two extracellular fluids such as cerebrospinal fluid and plasma.

MODE OF ACTION

It was early observed that the sulfonamides exert little bacteriostatic effect in the presence of pus, meat extract, yeast extract and other biologic mixtures — indeed, they are quite ineffective in the local or systemic treatment of walled-off purulent infections unless the pus can be drained. Woods⁸ tested the effect of various chemical reactions on the inhibiting power of yeast juice, and concluded that the inhibiting factor behaves exactly like *p*-aminobenzoic acid. This pure compound was in turn found to be a powerful inhibitor, interfering with the action of sulfanilamide when present in only one five-thousandth of the concentration of the drug. A practical result of this discovery has been the addition of *p*-aminobenzoic acid to the medium used for cultures in cases receiving a sulfonamide, to eliminate the possibility that the drug present may mask the presence of bacteria.⁹ A much more important outcome is the theoretical concept of competitive inhibition between sulfonamides and a metabolite, *p*-aminobenzoic acid, essential for the multiplication of the organism.⁸ Proof of this concept depends on evidence that *p*-aminobenzoic acid is an essential growth factor for sulfonamide-susceptible bacteria. Diligent search has disclosed very few organisms — and these nonpathogenic — in which *p*-aminobenzoic acid appears to be a growth factor^{10, 11}; for the rest it is necessary to assume that the organism synthesizes *p*-aminobenzoic acid to meet its normal

ments, but not enough to compete with bacteriostatic concentrations of sulfonamide drugs.

It is assumed in analogy to the participation of such vitamins as thiamine and niacin in oxidation-reduction enzyme systems that *p*-aminobenzoic acid is a vital link in some enzymatic mechanism. The sulfonamides on this assumption compete by possessing a chemical configuration that permits them to occupy a position in the enzyme that is ordinarily held by *p*-aminobenzoic acid, but lack the complete configuration necessary for the function of the latter. That *p*-aminobenzoic acid and the sulfonamides may be expected to be attracted to a similar position on an enzyme molecule follows from the extremely similar configurations of their structural formulas. Although the nature of the enzyme concerned is as yet completely unknown, the concept that sulfonamides act by competitive inhibition of an enzyme reaction is widely accepted.⁴

The bacteriostatic action of sulfonamides does not necessarily occur immediately, for it has been shown with *Escherichia coli* that multiplication takes place for about six cell divisions before it ceases in the presence of adequate concentrations of sulfonamides.¹⁴ The implications of this fact for the mode of action of the drug are not clear; it may possibly be related to the available stores of *p*-aminobenzoic acid. From a practical point of view, this emphasizes the importance of early treatment and may be one reason why overwhelming cases of meningitis or pneumonia are fatal in spite of treatment by a sulfonamide drug to which the organism is susceptible.

Considerable understanding has been gained by studying the bacteriostatic efficacy of a series of compounds derived from sulfanilamide by substitutions in the amide radical. Although the precise values reported for the drugs vary with the organism, medium and particular end point chosen, in vitro studies indicate that, in contrast to the early impressions, there is no specificity of any particular drug for a given organism.¹⁵ In the earlier studies on the physical chemistry of these drugs,^{16, 17} it appeared that the bacteriostatic power could be correlated with the extent to which the drug was ionized as an anion at the hydrogen-ion concentration of body fluids or ordinary culture media (pH 7.4). The degree of ionization is conveniently represented by the pK, which is the pH at which the drug is 50 per cent ionized. Thus, at pH 7.4 sulfathiazole (pK 7.1¹⁸) is largely ionized whereas sulfanilamide (pK 10) is ionized to the extent of only a fraction of 1 per cent and hence must be present in much greater concentration in order to be effective. This explains the excessive disproportion in the concentrations of sulfanilamide and *p*-amino-

benzoic acid competing with each other, since the latter is essentially completely ionized at pH 7. With recalculation in terms of concentration anions, *p*-aminobenzoic acid and various sulfonamides compete with each other in similar concentrations.¹⁷

Further work with new drugs showed this scheme to be an oversimplification, for when drugs were synthesized with pK values even lower than that of sulfathiazole, and consequently were even more completely ionized at pH 7.4 than is sulfathiazole, they were found to be less bacteriostatic.¹⁸ This can be explained by assuming a dependence of bacteriostatic potency on certain physicochemical functions (acidity of the anion¹⁹ or negativity of the sulfonamide group¹⁸) that vary with the pK, having a maximum value at about pK 6.8. These theories lead to the prediction that it will be impossible to synthesize a member of this series, working by the same mechanism, that will be more bacteriostatic than are sulfathiazole, sulfadiazine, sulfamerazine and certain other sulfonamides now in widespread clinical use, which have pK's at or close to the maximum. Efforts to improve on the present compounds must, then, be aimed at a reduction in toxicity, or at a change of structure so radical as to introduce a new mode of action.

The binding of sulfonamides to plasma proteins, which was discussed in connection with the problem of distribution in the body, was found to parallel the in vitro bacteriostatic potency of a series of sulfonamide compounds, the drugs with the greatest binding tendency being in general the most bacteriostatic.²⁰ This correlation suggests that the drugs in their assumed action by competition with *p*-aminobenzoic acid are bound to the hypothetical enzyme by the same forces that bind them to other proteins. Sulfamerazine and sulfamethazine, which have recently been found to be potent drugs, are all highly bound.²¹

RESISTANT STRAINS OF ORGANISMS

The bacteriostatic action of sulfonamides cannot involve an enzyme system that is universally present and susceptible in bacteria, since these drugs are effective against only a limited number of gram-positive and gram-negative organisms. Furthermore, certain patients have been found to be infected by drug-resistant strains of a number of ordinarily susceptible species of organism, where others have strains that become resistant during the course of prolonged exposure to moderate concentrations of the drugs in vitro or in vivo.²² The study of metabolic differences between resistant and susceptible strains appears to be one of the most attractive methods of probing further into the mode of action of the drugs. Certain sulfonamide-resistant strains of *Staphylococcus aureus* have been reported to synthesize *p*-aminobenzoic acid, which can be detected in the filtrate from the organisms.

*It has been noted that sulfanilamide inhibits the enzyme carbonic anhydrase,^{12, 19} which is responsible for the rapid conversion of carbonic acid or bicarbonate to free carbon dioxide in the body. This property accounts for the moderately depressed plasma carbon dioxide combining power sometimes noted in patients receiving sulfanilamide, but since the property is not shared by the other drugs in the series, it cannot be concerned in their bacteriostatic action.

but since the method of detecting this acid was biologic rather than chemical, it is not certain that the drug-inhibiting substance elaborated by the organisms was actually *p*-aminobenzoic acid.

In the study of earlier chemotherapeutic agents, it has been difficult to obtain direct evidence of the relation between resistance to treatment and variations in the host and in the infectious agent. With syphilis, indirect evidence indicates that in at least some cases resistance to treatment depends on factors in the host rather than on variations in the strain of the organism.²⁴ The effectiveness in vitro of sulfonamides has made it possible in many cases of gonorrhea and other diseases to place the responsibility for failure of therapy directly on the organism. With the gonococcus, a simple method has recently been developed for testing in vitro the response to sulfathiazole of each patient's strain of organism.²⁵ This permits accurate prognosis of the results to be expected from sulfonamide therapy and minimizes the time wasted before recognizing the desirability of other forms of therapy—for example, fever and penicillin—in sulfonamide-resistant cases. As the variety of available chemotherapeutic agents grows larger this principle will undoubtedly find ever-increasing application, especially with serious diseases where the saving of life may depend on early use of an effective drug.

TOXICITY

Even the best drugs now available give rise to toxic reactions, reported in as high as 10 to 15 per cent of some series, which are occasionally fatal. A large proportion of the toxic reactions of these drugs (except for the relatively soluble sulfanilamide) are due to the unusually large doses necessary and the low solubility of their acetyl derivatives. These properties, together with the high renal clearance of these compounds,^{26, 27} frequently lead to concentrations in the urine in excess of their solubility, with resultant crystallization in the tubules or ureters, renal damage results, but it is not clear whether all the toxic effects of sulfonamides on the kidneys arise from such precipitation. With drugs of which the degree of ionization varies significantly in the pH range of the urine—for example, acetyl sulfadiazine—the solubility can be markedly increased by rendering the urine alkaline. This type of toxic reaction can therefore be circumvented with certain drugs by administration of alkali.^{28, 29} Urea has also been shown experimentally to inhibit renal precipitation of the drugs.³⁰

The other toxic reactions are much less well understood and consist largely of primary toxic effects—for example, nausea, vomiting, headache and mental confusion—and a group of reactions that are usually delayed—hemolytic anemia, agranulocytosis, jaundice and drug fever, with or without a rash. Longcope³¹ has recently stressed the similarity

of the latter group to serum sickness, pointing out that although clinically these reactions of sulfonamides and other chemical drugs have many characteristics of sensitization phenomena, direct proof by demonstration of antibodies has not been obtained, and most workers have failed to demonstrate skin reactions to the drugs with any regularity. The unpredictability and persistence of these hypersensitive reactions present a contraindication to the use of these drugs in treating relatively trivial infections or in prophylaxis, and therefore limit their utility.

METABOLIC STUDIES

Although it has already been established that certain drugs act by inhibiting enzymatic activity,³²—for example, physostigmine inhibits choline esterase,—the present concept of the mode of action of sulfonamides by competitive inhibition of an enzyme provides a further thought-provoking link between drugs, vitamins and enzymes. It has already led to two important developments outside the field of chemotherapy. In the first place, *p*-aminobenzoic acid has been found to be an essential dietary factor in rats and chicks,^{33, 34} although evidence has been presented that this action may depend on stimulation of certain gastrointestinal micro-organisms to synthesize essential factors.³⁵ In the second place, competitive inhibition has been shown between other vitamins and structurally similar compounds, which behave as antivitamins. Thus the pyridine derivative of thiamine interferes with the growth of bacteria that require thiamine.³⁶ Similarly, nicotinamide and the co-enzyme derived from it have been observed to antagonize the effect of various sulfonamides on the growth of *Staph. aureus*,^{37, 38} whereas sulfapyridine and sulfathiazole (but not certain other sulfonamides) inhibit the stimulation of the respiration of the dysentery bacillus by nicotinamide or the co-enzyme.³⁹ The similarity of chemical configuration between nicotinic acid and sulfapyridine may not be an important factor in this antagonism, since the other sulfonamides that exhibit the reaction do not have the pyridine nucleus of these two compounds.

The metabolic effects of the sulfonamide drugs are not confined to bacteria. Evidence of the importance of antivitamins as well as vitamins in animal nutrition has been provided by the observation that sulfapyridine inhibits the curative action of nicotinic acid in dogs suffering from a deficiency of this vitamin.^{40, 41}

Sulfaguanidine and sulfasuxidine (succinyl sulfathiazole) are sulfonamide drugs with properties of solubility and absorption that permit high intestinal concentrations along with low concentrations in the body fluids. These drugs have been used in the treatment of certain types of enteric infection and in preoperative prophylaxis of peritoneal infection following gastrointestinal surgery. P

this practical utility, the drugs have provided an explanation for apparent differences in the vitamin requirements of various animal species. Whereas the concept of synthesis of vitamins by bacterial flora was first developed in relation to vitamin K, the suppression of such synthesis by these sulfonamide intestinal antiseptics has permitted the demonstration that biotin⁴² and folic acid^{43, 44} are essential for complete nutrition of the rat's tissues as well as of bacterial and animal species in which they have earlier been proved to be essential. The elimination of intestinal bacterial synthesis may be expected to provide further solutions of problems in vitamin research. The production of leukopenia and anemia in rats by these drugs permits a new experimental approach to the problem of blood dyscrasias.⁴⁴

An entirely new field of chemotherapy, not involving infections, has arisen from the observation that rats receiving huge doses of sulfonamides developed an enlargement of the thyroid gland shown to be due to interference with the response of the gland to the thyrotropic hormone of the anterior pituitary glands.^{45, 46} Further investigation of this phenomenon led to the development of other unrelated compounds, thiourea and thiouracil, that have proved useful in the treatment of hyperthyroidism, and that may in the future replace much of the surgical treatment of this disease.⁴⁷

* * *

Besides their great practical utility, the sulfonamide drugs have provided valuable fundamental advances in pharmacology and related fields, which may serve as a pattern for the study of the reactions of other drugs with the host and with the infecting agent. Their distribution in the body is primarily dependent on their degree of binding to plasma albumin, which in turn parallels their bacteriostatic power in its dependence on certain physicochemical functions of the acid-base dissociation constants of various members of the series. The antagonism between sulfonamides and a closely related chemical, *p*-aminobenzoic acid, has led to a theory of the mode of action of these drugs by competitive inhibition of a postulated bacterial enzyme. Para-aminobenzoic acid has subsequently been recognized as a vitamin in the nutrition of certain vertebrates, whereas the concept of competitive inhibition has led to the discovery of other antivitamin. Intestinal antiseptics by sulfonamides has made possible the discovery of new food factors essential in mammalian metabolism. Investigation of a toxic effect of massive sulfonamide therapy in animals has led to the development of other compounds that may significantly modify the treatment of hyperthyroidism.

The broad utility of sulfonamides has developed an unprecedented interest in the field of chemotherapy. It may be partly by virtue of this stimulation that penicillin, which lay relatively unrecognized for ten years following its discovery by Fleming

in 1929, has finally been found to surpass the sulfonamides in therapeutic effectiveness and freedom from toxicity. The development of other chemotherapeutic agents of microbial and synthetic origin offers future possibilities that may ultimately extend well beyond the range of infectious diseases.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30241

PRESENTATION OF CASE

A fifty-seven-year-old housewife entered the hospital because of pain in both sides of the abdomen.

The patient had been in apparent good health until two years before entry, when she experienced a knifelike pain in both lower quadrants of the abdomen. The pain caused the patient to double up and remained fairly severe for seven days. It was more marked on the left than on the right, was spasmodically crampy and did not radiate. Within six hours of the onset of illness, she developed nausea and vomited greenish material, without any gross blood, coffee-grounds or fecal material or recognizable food. The vomiting was followed by "watery diarrhea" in which no blood or mucus was apparent. She had no chills or fever. She was seen by her physician, who prescribed pills and bed rest. The symptoms disappeared in about two weeks, and she felt "fine" during the ensuing seventeen months.

Seven months before entry she had recurrence of the pain in the lower abdomen. This time, however, the pain was dull, not crampy, and of much less intensity according to one story, but crampy and knifelike by another. It involved both lower quadrants, but was a little more pronounced on the left than on the right, and radiated to the vagina and to both flanks. She vomited greenish material and had diarrhea productive of bright red blood and mucus. This apparently lasted for several hours, but these attacks recurred on the average of once a month, continuing one or two days but without blood in the stools. Between the attacks she felt weak and had a poor appetite. During the

last month before entry, the pain became almost constant and there were bouts of diarrhea, the last episode occurring two days before admission. She had lost 30 pounds in six months. There had been no disturbance of urination.

She had had an appendectomy and a bilateral oophorectomy twenty-four years before admission.

Physical examination showed a well-developed, obese woman in no discomfort. The heart and lungs were normal. There were a sense of resistance and an indefinite mass in the suprapubic region. Rectal and pelvic examinations were negative.

The blood pressure was 130 systolic, 90 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 2,850,000, with 65 per cent hemoglobin. The white-cell count was 6900, with 74 per cent neutrophils. The urine was negative. One stool examination was guaiac negative. The nonprotein nitrogen was 25 mg. per 100 cc., and the protein 6.1 gm.; the blood chloride was 109 milliequiv. per liter. A blood Hinton test was negative. Proctoscopic examination was unsatisfactory in that the proctoscope could not be passed into the sigmoid, but so far as could be seen the mucosa was normal. A barium enema showed a pressure defect on the medial aspect of the cecum, which was thought to be due to an extrinsic mass. The terminal ileum could not be filled. The cecum was quite spastic, and could not be filled satisfactorily. A gastrointestinal series was unsatisfactory because of technical difficulties. Fluoroscopically, the esophagus, stomach and duodenum were negative. The motor meal passed easily to the lower ileum and proximal colon. Several loops of the ileum were slightly dilated. The terminal 10 cm. appeared definitely narrow, and the mucosal pattern was not visible (Fig. 1). There was some swelling of the ileocecal valve, and a definite constant deformity of the cecum. A repeat barium enema showed ready filling of the colon. The cecum was spastic, but no constant defect or evidence of pressure on the cecum was seen. No barium entered the terminal ileum. An intravenous pyelogram was negative.

Following admission the patient had vomiting and pain in the lower abdomen for a day or two, but these disappeared. On the eleventh hospital day a sigmoidoscopy was introduced through the Miller introduced a sigmoidoscope into the rectum and showed a lesion in the terminal

and cecum. No definite shelf could be seen. The mucosal pattern was partially preserved, and there was some swelling of the ileocecal valve. She was given several transfusions, and on the fifteenth hospital day an abdominal exploration was performed.

DIFFERENTIAL DIAGNOSIS

DR. HORACE K. SOWLES: Apparently from the story the cramps two years before entry were of a mechanical nature. The recurrent pain in the lower

shown a lesion in the terminal ileum. This could have accounted for her type of symptoms, because she might have had temporary obstruction or partial intussusception at the ileocecal valve, which caused the attacks of pain and vomiting and also, on one occasion, blood in the stools.

The lesions of the terminal ileum are not many. There was apparently no evidence in the x-ray films to suggest regional ileitis, tuberculosis or ulcerative colitis. Perhaps it was a tumor of the terminal

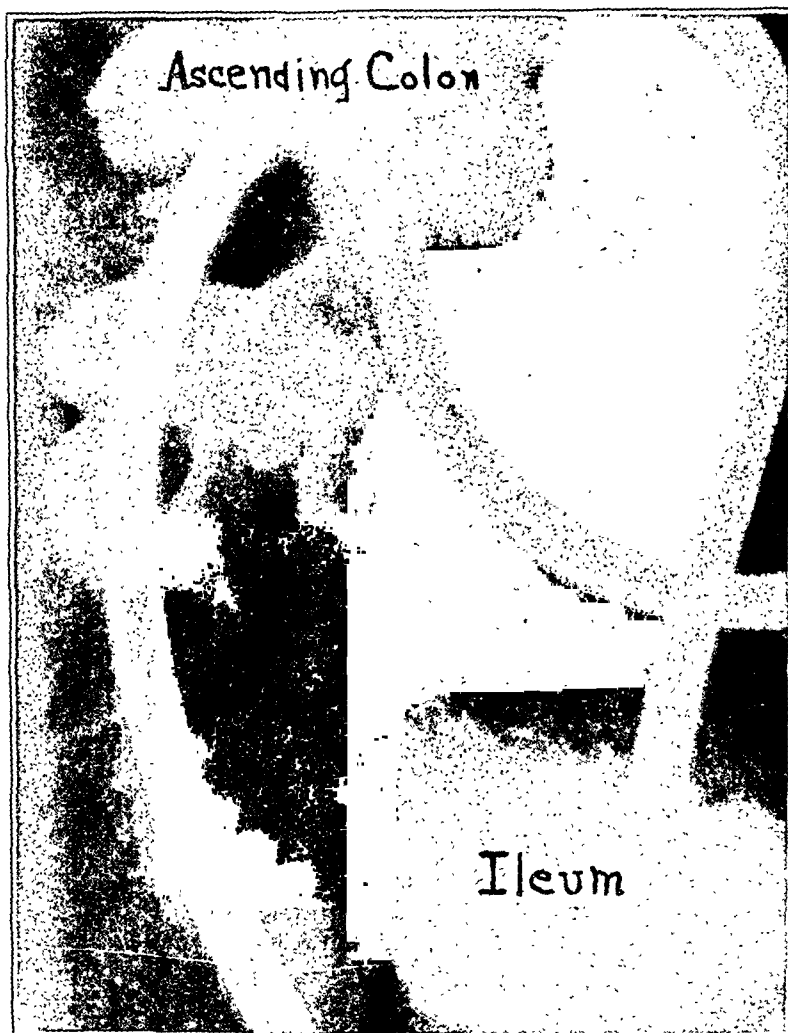


FIGURE 1. Spot Film of the Ileocecal Region Showing the Lesion at the Terminal Ileum.

abdomen was of the spasmodic type, and there was no fever. Seven months before entry she had a recurrence of these attacks.

The laboratory findings on entry were normal, with the exception of the red-cell count and hemoglobin, which showed a definite anemia. The physical examination was noncontributory. The barium enema, however, revealed a definite lesion. On one occasion the x-ray examination showed something at the cecum that may have been extrinsic, although that was not confirmed on the second examination. The second observation seems to have

ileum, such as a sarcoma or carcinoma. They are rare, but they do occur. A small tumor in the terminal ileum can easily cause intussusception, which would explain the pain but not the severe secondary anemia. One does not usually see a marked anemia like this with lesions of the terminal ileum. It does, however, occur with carcinoma of the cecum; but the x-ray report says that the cecum was normal. The patient had a secondary anemia and a marked weight loss, so my first guess is malignant disease of the ileocecal valve, and my second choice, regional ileitis, which does not explain the loss of

weight and the anemia so well as carcinoma. Tuberculosis is unlikely. I do not believe that it could have been anything in the pelvis.

In passing, the commonest extrinsic mass around the cecum is an appendiceal abscess, which is not possible in this case because of the previous appendectomy. Furthermore, there is nothing in the history that suggests it.

DR. BENJAMIN CASTLEMAN: Would you like to look at the x-ray films?

DR. SOWLES: Yes; perhaps the roentgenologist can tell me something that will change my opinion.

ANATOMICAL DIAGNOSIS

Malignant carcinoid of ileum, with metastases to regional lymph nodes.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The clinician in charge of the patient leaned, I believe, toward regional ileitis rather than tumor. At operation the surgeon felt a mass in the region of the terminal ileum and resected the terminal ileum, the cecum and part of the ascending colon. The terminal ileum was markedly

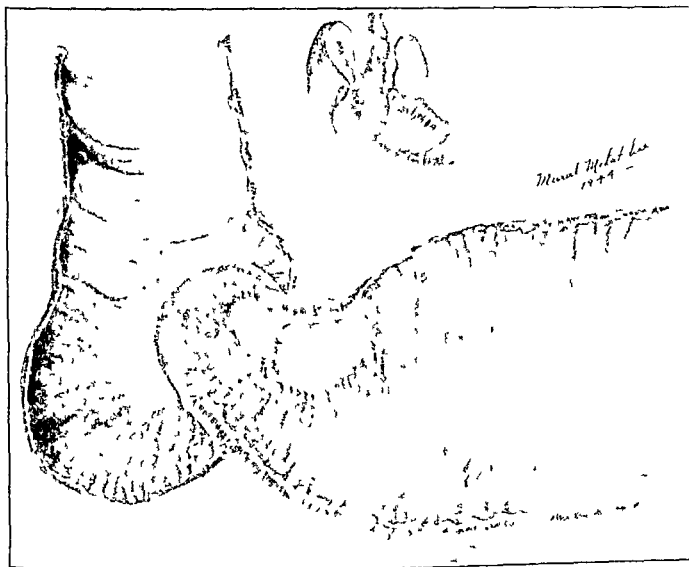


FIGURE 2. Drawing Showing the Lesion in the Terminal Ileum

The insert represents a cross section of the tumor, with neoplastic tissue above and below the muscularis.

DR. MILFORD SCHULZ: These films demonstrate a lesion in the terminal ileum. The persistent irregularity of the cecum looks more like spasm than infiltration. The mucosal pattern in the terminal ileum is somewhat altered.

DR. SOWLES: If the lesion was a carcinoma, it probably arose in the ileocecal valve, the thickening of the terminal ileum being due to edema. Such lesions are not, as a rule, primary in the ileum.

CLINICAL DIAGNOSIS

Regional ileitis.

DR. SOWLES'S DIAGNOSIS

Tumor at ileocecal valve, probably carcinoma.

dilated. Just proximal to the ileocecal valve, there was a 3-cm mound-like tan lesion, composed of nodules that were covered with a thin layer of mucosa (Fig 2). These nodules extended on to the edematous tip of the valve, which protruded into the cecum for about 3 cm. On cross section some of the nodules extended through the muscularis into the serosa.

At this point, would you like to commit yourself further, Dr. Sowles?

DR. SOWLES: My idea that the pain was due to partial intussusception is proved by the findings. Of course, the commonest cause of intussusception, except in small children, is a tumor of the bowel wall, which is a nucleus for the intussusception. I suppose that it could have been a

I should think that, because of the marked anemia, she must have had malignant disease of the carcinomatous type.

DR. CASTLEMAN: The tumor involved the entire mucosa, submucosa and muscularis, extended into the serosa and was also present in the adjacent lymph nodes (Fig. 3). All the tumor cells were uniform in size, perfectly round and grouped in masses. The appearance is characteristic of a carcinoid or argentaffinoma—a tumor that arises from the argentaffin cells of the small intestine. These tumors are usually benign, but in perhaps



FIGURE 3. Photomicrograph of a Metastatic Lesion in a Regional Lymph Node.
Note the characteristic carcinoid cells.

less than half the cases they metastasize to the regional nodes, where the cells may remain for years without going any farther. They are not uncommon incidental autopsy findings if they are hunted for. The tumors invade the mucosa, but ulceration rarely occurs.

The involvement of the lymphatics in the wall of the bowel and of the regional nodes makes this case a malignant carcinoid. In addition, at operation the surgeon felt a mass in the liver, so it had apparently gone farther than the regional nodes. We have had in the past, I believe, two or three other cases in which the tumor had metastasized farther than the regional lymph nodes, but it is extremely rare. I should think that, even though

the patient had a mass in the liver, the prognosis is good for a number of years. These tumors grow extremely slowly. I recall a patient on whom the late Dr. Daniel F. Jones operated for small-bowel obstruction, finding a tumor with a large adherent mesenteric mass of metastases. He resected the small bowel, but left the metastases. This was in 1913, before these tumors were separated from carcinomas, although Dr. J. Homer Wright in his surgical report said, "The arrangement and appearance of these cells suggest the type of cancer that is found in the appendix." The man died twenty years later at this hospital following a prostatic operation, and at autopsy there were the same masses of nodes that Dr. Jones had left in. Some had become calcified, but microscopically they showed carcinoid.

CASE 30242

PRESENTATION OF CASE

A sixty-six-year-old man entered the hospital because of "bladder trouble."

For many years the patient had a great deal of "bladder trouble." About fifteen years before entry he had a left nephrectomy for "pus in the kidney." Following this, his condition improved for a year or two, but then he developed frequency and urgency of urination, with pain and burning. He had aches and pains in the region of the right kidney. About four or five weeks before entry, following a prostatic massage by his physician, he experienced increasing burning, frequency and urgency. There was no change in the urinary stream. The urine was cloudy. He had had no chills or fever.

He had had a chronic cough productive of yellowish-white, thick sputum for many years. For four years before entry he had had shortness of breath on exertion and orthopnea. About seven months before entry he developed ankle edema and "fluid in the lungs." He was put on $1\frac{1}{2}$ gr. of digitalis daily, but the time was reduced to every other day because of an episode of nausea and vomiting. Dyspnea on exertion continued. About two weeks before admission he was seen in the Emergency Ward because of urinary difficulty.

Examination showed considerable difficulty on breathing, with prolonged expiration. The chest was emphysematous. The lungs were full of coarse wheezes. There was tenderness over the bladder. Rectal examination revealed a small nontender prostate, but the base of the bladder and the surrounding areas were exquisitely tender.

The blood pressure was 115 systolic, 70 diastolic. The temperature was 98°F., the pulse 80, and the respirations 30.

The urine was cloudy, with a pH of 6, a specific gravity of 1.010, and a ++ test for albumin. The

sediment contained numerous white cells and occasional red cells.

The patient was given hot sitz baths, demerol and sandalwood oil. He was also given 10 drops of a saturated solution of potassium iodide three times a day, $3\frac{3}{4}$ gr. of aminophyllin four times a day by mouth and $1\frac{1}{2}$ gr. of digitalis daily. Following this, the dyspnea and orthopnea disappeared. Although there was some relief of urinary trouble, he was still in considerable discomfort because of pain and burning on urination. Two days before admission to the ward he developed "an asymptomatic morbilliform and acneform rash over the entire body and a conjunctivitis." He had had no chills or fever.

Examination on admission showed a patient who looked sick and complained of pain in the bladder. He was not dyspneic. There was a diffuse morbilliform and acneform rash over the face, neck, arms and trunk. Moderate conjunctivitis and a yellow discharge were seen in both eyes. The pupils were small and fixed. Some moist rales and intermittent rhonchi were heard in both bases. The chest was emphysematous. The heart was of normal size. The sounds were distant, and a slight systolic murmur was heard over the precordium. A tender mass, measuring 6 by 7 cm., was palpated in the right flank that seemed to have some connection with the liver and that was finally believed to be a Riedel lobe of the liver. The edge of the liver extended 4 cm. below the costal margin and was tender. There was exquisite tenderness over the prostate and bladder.

The blood pressure was 90 systolic, 40 diastolic. The temperature was $102^{\circ}\text{F}.$, the pulse 120, and the respirations 30.

Examination of the blood showed a red-cell count of 3,700,000, with 18 gm. of hemoglobin. The white-cell count was 15,300, with 72 per cent neutrophils. The urine contained many white cells and gave a +++ test for albumin.

Potassium iodide was stopped. He was given 2 cc. of Cedilanid intravenously, followed by 100 cc. of aminophyllin intravenously. The skin rash disappeared in twenty-four hours, but the patient's general condition seemed worse. The lungs showed many moist rales. He developed fecal and urinary incontinence and became unresponsive. The non-protein nitrogen was 60 mg. per 100 cc. He was given intravenous fluids and 1.25 gm. of sulfadiazine intravenously. A Foley catheter was placed in situ. He became anuric, developed marked abdominal distention and Kussmaul breathing, and died on the third hospital day.

DIFFERENTIAL DIAGNOSIS

DR FLETCHER H. COLBY: Here is a patient with a long story of bladder trouble. First of all, I think it is reasonable to exclude malignant disease because of the long duration of the symptoms. The outstanding complaint was bladder irritability. In

addition to this the patient had some sort of chronic disease, with emphysema or possibly bronchiectasis, which perhaps put a severe load on his heart, so that he had a certain amount of cardiac difficulty. In all probability that is aside from the main issue—the bladder trouble.

The patient went to the Emergency Ward two weeks before he entered the hospital, complaining of his bladder. When he entered the hospital his chief difficulty concerned the bladder. What are the things that may give long-continued bladder irritability? First of all are the local conditions, infection, residual urine from some obstruction to the free flow of the urine and complete emptying of the bladder, such as stricture or enlarged prostate. These seem to have been eliminated because there had been no change in his ability to void. A vesical calculus may cause irritability and infection. Diverticulum of the bladder with infection may also cause considerable irritability of the bladder. This man, however, had had sufficient local symptoms, with tenderness on pressure over the bladder, to suggest even a pericystitis, involvement of the perivesical tissues, in addition to possible local lesions in the bladder, causing marked, continued, chronic irritability.

There is also the upper urinary tract to be considered, and it is reasonable to look there seriously for the source of the trouble. It is quite obvious that infection of some sort played a major role in this patient's illness. We have no x-ray films, which would be helpful, but we have to get along with the information given to us. He had had a nephrectomy years ago, and at the time of entry probably had involvement of the remaining kidney. The 6-by-7-cm. mass felt in the right upper quadrant was possibly the right kidney rather than the right lobe of the liver.

The conditions that may involve both kidneys are not many. In the first place there are the various congenital abnormalities that result in inadequate drainage of the kidney, such as aberrant vessels and kinks and so forth in the ureters, with hydronephrosis. The kidney that had been removed was said to be a "pus kidney." He might have had the left kidney taken out for a calculus pyonephrosis, and on entry he might have had stones and infection on the other side. Pyelonephritis does not sound reasonable. Any of these conditions may cause long-standing bladder irritability, and almost any one of them can be associated with perirenal infection, which may not be evident on examination. The most obvious lesion, however, to account for long-continued bladder irritability, the involvement of one kidney, with removal, and finally the involvement of the other kidney, is renal tuberculosis. Renal tuberculosis may stay dormant in one kidney for a many years. I saw a patient at the Lakeside Hospital who, after having had a nephrectomy for tuberculosis, was

I should think that, because of the marked anemia, she must have had malignant disease of the carcinomatous type.

DR. CASTLEMAN: The tumor involved the entire mucosa, submucosa and muscularis, extended into the serosa and was also present in the adjacent lymph nodes (Fig. 3). All the tumor cells were uniform in size, perfectly round and grouped in masses. The appearance is characteristic of a carcinoid or argentaffinoma—a tumor that arises from the argentaffin cells of the small intestine. These tumors are usually benign, but in perhaps



from the record. An interesting feature is that the disease simulated heart failure, with shortness of breath; in fact, he had been treated for heart failure, having received digitalis and bed rest, but the dyspnea and orthopnea increased. Probably at the final entry he did have heart failure. He did not respond to aminophyllin or digitalis, and potassium iodide caused apparent toxic irritation. That sort of picture can simulate heart failure. It might be labeled a pulmonocardiac picture. The patient had emphysema, and yet all the evidence is against heart disease, because the heart was normal in size; the blood pressure was normal (115 systolic, 70 diastolic) before he went into collapse. The red-cell count was 5,700,000 and the hemoglobin 18 gm., which was a compensatory mechanism for the red cells in the lung circuit to make up for the emphysema. This was not a true polycythemia.

Coming back to the tender mass, I think it was a hypertrophied kidney diseased with tuberculosis.

DR. COLBY: Dr. Butler has just whispered an important differential factor. Pyogenic infection of the upper urinary tract or of the bladder itself, such as an infected diverticulum, usually does not cause such protracted and distressing bladder symptoms and such tenderness as does tuberculosis.

DR. ALLAN M. BUTLER: The bladder irritation in the presence of long-continued renal infection is the thing that places the emphasis on this being tuberculosis.

DR. JOSEPH C. AUB: I saw this man in the Emergency Ward, and I thought that the mass was a big liver. Secondly, the severe pain was in the prostate and around it rather than in the bladder, and I assumed that he had prostatic abscess, which might have ruptured. He had an infection and was in uremia. I thought that he had pyelonephritis from

the patient had a mass in the liver, the prognosis is good for a number of years. These tumors grow extremely slowly. I recall a patient on whom the late Dr. Daniel F. Jones operated for small-bowel obstruction, finding a tumor with a large adherent mesenteric mass of metastases. He resected the small bowel, but left the metastases. This was in 1913, before these tumors were separated from carcinomas, although Dr. J. Homer Wright in his surgical report said, "The arrangement and appearance of these cells suggest the type of cancer that is found in the appendix." The man died twenty years later at this hospital following a prostatic operation, and at autopsy there were the same masses of nodes that Dr. Jones had left in. Some have become calcified, but microscopically they showed carcinoid.

CASE 30242

PRESENTATION OF CASE

Cystitis, acute and chronic. the hospital.
Pulmonary tuberculosis, healed, apical.
Pulmonary emphysema.
Bronchiectasis, slight.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The remaining kidney was not particularly large. The upper pole was sclerotic; the lower pole was smooth and somewhat enlarged and, on section, proved to have several reddish-yellow caseous areas. It was suspicious of tuberculosis, but we were not sure at the time of autopsy. The prostate had several small greenish-black abscesses without gross evidence of caseation, such as was present in the kidney. Microscopic sections, however, showed tuberculosis in both the prostate and the kidney. Sections from the bladder, which in the gross was markedly injected and trabeculated, showed no evidence of tuberculosis. The lungs showed healed tuberculosis at the apices, without any evidence of activity. There was a fair amount of emphysema, and in one lower lobe some bronchiectasis.

DR. CHAPMAN: How much bronchiectasis?

DR. CASTLEMAN: Very slight. There was some edema and congestion of the lungs, but no evidence of pneumonia.

DR. AUB: How about the liver?

DR. CASTLEMAN: It was enlarged, and showed marked fatty change. The big mass that was felt was undoubtedly the liver and not the kidney.

DR. JAMES M. NEIL: What did the heart show?

DR. CASTLEMAN: It was normal.

DR. CHAPMAN: You think that the patient died primarily of uremia?

DR. CASTLEMAN: Probably.

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THE JOURNAL does not hold itself responsible for statements made by any contributor.

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"FOOD FIGHTS FOR FREEDOM"

"Food," according to an alliterative slogan currently popularized by our federal nutritionists, "fights for freedom." We are reminded of the similar cliché of twenty-six years ago, "Food will win the war." The new slogan, as compared with the old, does not represent any particularly original idea, but neither does the fundamental principle on which it is based; when the producers of food leave their plows in the furrows and take up their muskets, food becomes a peculiarly precious commodity. That which is almost taken for granted by a large proportion of the population in a still fertile country in times of peace becomes another weapon with which to fight when the country goes to war.

This sudden relative scarcity of life's indispensable fuel brings into an embarrassing limelight certain interesting jugglings with the nation's food supply that are too easily overlooked in normal times when everyone, like the king in Milne's whimsical verse, had a little bit of butter for his bread. Many of our readers will no doubt recall the chapter and verse:

The Dairymaid
She curtsied,
And went and told
The Alderney:
"Don't forget the butter for
The Royal slice of bread."
The Alderney
Said sleepily:
"You'd better tell
His Majesty
That many people nowadays
Like marmalade
Instead."

Times, however, can change. Many people nowadays are being reminded by new governmental agencies, different from those that had helped to suppress it, that oleomargarine fortified with vitamin A is a food the equal in every respect, except perhaps for certain esthetic values, of natural (if sometimes artificially colored) dairy butter. Oleomargarine, moreover, if accepted on the basis of its cost of production, should sell for half the price of butter; an ideal food for the low-income groups in normal times — satisfactory for anyone in difficult times.

Here enters pressure politics, one of the black spots of our democratic system, for in practically every state of the Union where margarine competed seriously with the sale of butter, as well as in the Congress of the United States, laws have been enacted to nullify the economic laws of such free competition. Thus, the Bureau of Internal Revenue is authorized to levy an excise tax on every merchant selling the product, and every state has added one or another type of restrictive legislation, such as taxes ranging from 5 to 15 cents a pound, license fees for manufacturers and vendors and, in some instances, special licenses for restaurants and hotels serving margarine to their patrons.

It was only recently, indeed, that the embattled farmers of Wisconsin rose in their wrath against a scientific investigator in their tax-supported uni-

versity who had dared to make public his findings in favor of margarine as a food substance! Thus does an entrenched interest show that sometimes food can fight against freedom.

ARTHROPOD CONTROL

ARTHROPODS such as bedbugs, ticks, mosquitoes and house, stable and deer flies are well known as pests by civilians in this country, and the role played by certain species of arthropods, such as ticks, mites and biting insects, in the transmission of disease is well appreciated by the medical profession. Previous to the present war, the development of insecticides and newer methods of controlling arthropod vectors of disease was being investigated on a smaller scale than was deserved by the immensity and importance of the problem for the protection and betterment of the public health. The present war, with its widespread outposts and fighting throughout tropical and subtropical areas, brought to the fore the urgent need for better and more effective methods of arthropod control, if major and possible disastrous epidemics of certain parasitic, rickettsial, bacterial and virus diseases were to be prevented.

The challenge of the emergency was accepted by the combined intelligence and efforts of medical officers, entomologists, chemists and sanitary engineers. The foresight of this method of attack is now beginning to show successful results. Obviously much of the experimental evidence and procedures developed in the laboratory and the field will have to remain unknown until the end of the war. Certain of the newer developments for arthropod control, however, are reflected in published accounts, particularly those concerning the control of mosquitoes that transmit malaria.^{1, 2}

Russell² has reviewed the various methods of controlling mosquitoes now in use among the armed forces, methods that he had a great share in developing and applying in the Philippines and India. The measures for military malaria control are applicable both to fixed installations, such as camps, and to field operations. In addition to the well-known methods of controlling mosquitoes by screening, the destruction of larvae and the use of sleeping nets, methods for the spray killing of adult mosquitoes

and keeping them away with repellents are now effective.

Methods for the spray killing of adult mosquitoes were given an effective trial in Africa by De Meillon³ and Ross.⁴ Since that time they have been widely used in India,⁵ and have been extremely successful in reducing the transmission of malaria.⁵ The spray for the disposal of the effective agent, extract of pyrethrum flowers, may be applied with small household spray guns and paint-gun sprayer assemblies or from pressure cans or cylinders. Application in the form of an aerosol from pressure cylinders is becoming increasingly useful both in the field and for effective spraying of aeroplanes arriving from tropical areas. Effectiveness against the tsetse fly,⁶ the vector of sleeping sickness, is particularly fortunate because of the great danger of introducing this insect to South America in much the same way as the highly efficient malaria vector, *Anopheles gambiae*, was introduced some years ago in Brazil.

The pyrethrum sprays are contact poisons, killing all species of mosquitoes and certain other insects by a destructive action on the central nervous system. These sprays are nontoxic to man and lower animals, although some irritation and inflammation may be caused by direct contact on the skin.

Mention should also be made of mosquito repellents, which are said to be effective for at least four hours. Two of these listed by Russell² are known as "612" (Everready) and dimethylphthalate (Skat).

Just how soon some of the above compounds will be released for civilian use will depend no doubt on the length of the war. It should be appreciated, however, that the war has stimulated research in a field that needed development, thereby helping in more efficient control of arthropod-borne diseases and also providing the civilian with an eventual means of alleviating suffering from the bites of the ubiquitous mosquito.

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MASSACHUSETTS MEDICAL SOCIETY

AWARD FOR VALOR

Major John W. Henderson, M.C., A.U.S., of Worcester, was recently awarded the Silver Star for gallantry in action near Alimena, Sicily, on July 22, 1943. The citation reads: "Besieging enemy forces had forced our troops to withdraw. Under cover of darkness, he successfully led a searching party well forward of the outposts to locate and evacuate casualties. His outstanding courage and coolness under heavy enemy fire merit the highest praise."

William D. Ducey of Brockton, because of gross professional misconduct in the practice of his profession as shown by his conviction in court.

H. QUIMBY GALLUPE, M.D., Secretary
Board of Registration in Medicine

State House
Boston

REPORT OF MEETING

NEW ENGLAND PATHOLOGICAL SOCIETY

The first meeting of the year of the New England Pathological Society was held in the Amphitheater of the Mallory Institute of Pathology on Thursday evening, January 20.

The first paper was given by Dr. Maxwell Finland, the title being "Clinical and Physiologic Aspects of Conflagration Injuries of the Lungs and Air Passages." Respiratory complications of conflagration injuries, as judged from clinical observations in the cases from the Cocoanut Grove disaster, vary markedly in severity. The mildest cases may show nothing more than slight cough and irritation of the throat. The next grade of severity is manifested by laryngitis without evidence of pulmonary damage. Then there may be laryngotracheobronchitis, as evidenced by hoarseness, cough, sputum and scattered musical rales. Pulmonary involvement of varying extent is manifested by these signs and, in addition, by increasing numbers of rales scattered throughout the lungs and, later, by atelectasis of varying extent and by signs of small areas of consolidation. The severer cases have more extensive rales with proportionally greater degrees of dyspnea and cyanosis. In such cases, there usually is considerable stridor, which may be severe enough to necessitate tracheotomy or bronchoscopic suction of the larynx and trachea. Such suction is productive of thick mucoid material that may contain fibrous membranous structures of varying size. The aspirated material also contains ciliated epithelial cells and many carbon particles.

Practically all cases with injuries to the respiratory tract also have burns of the face and nose. In general, the severity of the respiratory damage is correlated fairly closely with the extent and severity of the surface burns. In those cases from the Cocoanut Grove fire in which there was a great discrepancy between the extent of the surface burn and the severity of the respiratory damage, a story of some attenuating circumstance was usually discovered to account for discrepancy. For instance, some patients with extensive surface burns had covered their faces and noses with wet cloths and had avoided respiratory injury in that way; whereas those who were well clothed, or were stampeded and found themselves beneath other people, had extensive respiratory damage without surface burns.

No single cause of the respiratory injury could be determined. All the patients with the severest pulmonary damage had apparently had prolonged exposure after having become unconscious within the burning building, the loss of consciousness probably being due to excessive amounts of carbon monoxide. In this state the patients presumably inhaled hot noxious fumes that contained products of incomplete combustion of organic materials containing carbon and nitrogen. Some of these products are known to be pulmonary irritants. Interestingly enough large volumes of plasma, physiologic saline solution and other fluids were given to almost all the patients who had severe respiratory damage without apparently producing or increasing pulmonary edema to any appreciable extent. These studies were carried out with the collaboration of Dr. C. S. Davidson, of the Thorndike Memorial Laboratory, and Dr. Stanley Levenson, resident surgeon to the Burn Assignment of the Surgical Services, Boston City Hospital.

In the discussion that followed, the question of the clinical effect of nitrous oxide was raised. If this had been present, in Dr. Finland's opinion, the findings would have been similar to those seen in the Cleveland disaster, in which the patients exhibited more upper respiratory symptoms than those referable to the tracheobronchial tree.

The next paper was entitled "Pathology of Conflagration Injuries to the Respiratory Tract" and was given by Stanley Leary. He reported the findings in the Cocoanut Grove victims. The Pathological Department of the

CORRESPONDENCE

DEPRIVATION OF LICENSES

To the Editor: At a meeting of the Board of Registration in Medicine held on April 12 the Board voted to revoke the license of Dr. Matthias V. Bridges, 41 Buckingham Road, North Andover, Massachusetts, to practice medicine in the Commonwealth because of his conviction in court.

H. QUIMBY GALLUPE, M.D., Secretary
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held May 17, the Board voted to revoke the registration to practice medicine in this Commonwealth of Dr. Ray D. Hester, West Warren, Massachusetts, because of gross misconduct in the practice of his profession as shown by his conviction in court.

H. QUIMBY GALLUPE, M.D., Secretary
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held May 17, the Board voted to revoke the license to practice medicine in this Commonwealth of Dr. Lizzie Osgood, 42 North Street, Pittsfield, Massachusetts, because of a mental condition.

H. QUIMBY GALLUPE, M.D., Secretary
Board of Registration in Medicine

State House
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To the Editor: At a meeting of the Board of Registration in Medicine held May 17, the Board voted to revoke the license to practice medicine of Dr. Ralph Coleman, 174 Central Street, Lowell, Massachusetts, because of gross misconduct in the practice of his profession.

H. QUIMBY GALLUPE, M.D., Secretary
Board of Registration in Medicine

State House
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To the Editor: At a meeting of the Board of Registration in Medicine held May 17, the Board voted to revoke the license to practice medicine in this Commonwealth of Dr. Harry Weintraub, 327 Salem Avenue, Malden, because of gross misconduct in the practice of his profession as shown by his conviction in court.

H. QUIMBY GALLUPE, M.D., Secretary
Board of Registration in Medicine

State House
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To the Editor: At a meeting of the Board of Registration in Medicine held May 17, the Board voted to revoke the license to practice medicine in this Commonwealth of Dr.

Hospital and of the Medical Examiner Service of Suffolk County at the Mallory Institute of Pathology. According to the studies of Mr. Frank Stratton and Dr. W. W. E. Jetter, the blood from 9 of 10 victims dying at the club revealed a saturation with carbon monoxide adequate to account for the deaths. In 6 victims who died at the club there was injection of the mucosa of the upper tract with punctate hemorrhages, as well as hemorrhagic edema of the widely distended lungs.

Among the hospitalized victims the outstanding symptoms were respiratory and were responsible for the high mortality. The lesions involved the upper tract and the terminal bronchioles, atria and alveoli. In the literature, the only similar conflagration injuries were reported from a German munition factory in 1917; this was associated with a flash fire with heavy smoke among women filling hand grenades, and the mortality was 50 per cent.

Lesions in the victims comprised minor visible burns, including the nares, and pseudomembrane formation in the larynx and upper trachea; there was less effect in the lower trachea but in some cases, necrosis of the bronchial walls and pseudomembrane formation was present. Lesions of the lung parenchyma were focal, but with hemorrhage and fibrin formation in most cases rather than purulent bronchopneumonia. The polymorphonuclear reaction was less than expected, as though negative chemotaxis was being exerted. Nonoccluding thrombi in veins were frequent. Occluding venous thrombi with infarcts were present in 3 cases. The victims who survived the first few days tended to show only slight lesions (injection and hemorrhage) of the upper tract; the lungs evidenced massive edema in some cases, but focal lesions of the terminal bronchioles and parenchyma were found in all dying within twelve days after the fire. The lungs in general were distended, atelectasis was not marked, the bronchi were dilated, air was trapped focally and there was less emphysema than expected.

Dr. Valy Menkin in discussing the paper stated that the findings were characteristic of the necrosin effect, with necrosis and fibrin thrombosis of veins. The liberation of euglobulin was, he thought, responsible for the bed fever. The absence of marked neutrophilic infiltration did not mean the absence of an acute inflammatory process but was a phenomenon of gradation. Possibly lactic acid formation prevented the emigration. Dr. Leary stated that, although the neutrophilic reaction was not the usual type of response, the lesion was nevertheless inflammatory in type. In response to a question by Dr. Reuben Z. Shultz concerning the type of injury seen in cases of immediate death, Dr. Leary said that death was due to carbon monoxide poisoning with injected overdistended lungs.

The last paper was by Dr. Alan Moritz and was entitled "An Experimental Study of Thermally Induced Injuries of the Lungs and Air Passages of Dogs." Dry and moist air at initial temperatures varying between 100 and 1000°C. was conducted to the larynx of anesthetized dogs through an insulated glass cannula. By means of an electrical heating unit, the inner wall of the cannula was maintained at a minimum temperature of between 100 and 125°C. to reduce heat loss between the external source of heat and the larynx. In some experiments the inhalation of hot air occurred incident to the normal respiratory activity of the animal, and in others hot air was forced into the lungs by a pump in such a way as to simulate the rate and amplitude of respiration. Thermocouples were placed in the larynx and at the bifurcation of the trachea to record the temperature of the inhaled air.

It was observed that moist air at 100°C. was more likely to produce pulmonary injury than dry air at 1000°C. Even with an initial external temperature of 1000°C., dry air was cooled to between 500 and 600° at the larynx and to between 60 and 80° by the time it reached the bifurcation of the trachea. The principal if not the only pulmonary changes produced by the inhalation of hot dry air were hyperemia and focal atelectasis due to the aspiration of detached masses of necrotic tracheal mucous membrane.

Superheated moist air (100 to 125°C.) produced direct pulmonary injury in the form of a necrotizing bronchitis with interstitial and intra-alveolar pneumonia of the central portions of all lobes, interstitial and intra-alveolar hemorrhage, and pulmonary edema.

In normal circumstances the inhalation of superheated air, dry or moist, would not be expected to produce significant pulmonary disturbance except in association with severe

burns of the skin and of the mucous membranes of the nose or mouth and an obstructive edema of the larynx. Primary injury not associated with burning of the skin of the face and of the mucosa of the nose and mouth, or with laryngeal edema, is not likely to be of thermal origin.

In response to a question concerning the length of exposure, Dr. Moritz said that with heated air, the exposures were up to 100 respiratory cycles over a period of four seven minutes. With steam, the exposures were approximately forty seconds. In answer to another question, he stated that the effect of hot air was greatest in the upper portion of the trachea, where the heat was given up most rapidly. There was also considerable discussion about the location of the edema of the larynx. In animals, Dr. Moritz found the picture to be variable, depending on the amount of areolar tissue present in the different areas. This tissue is especially loose on the esophageal surface of the larynx. Dr. Leary stated that, in his experience, the most marked edema in man was in the aryepiglottic folds.

BOOKS RECEIVED

The receipt of the following books is acknowledged and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Life Is Too Short: An autobiography. By C. Kay-Ser (Frederick Creighton Wellman, M.D.). 8°, cloth, 348 pp. Philadelphia: J. B. Lippincott Company, 1943. \$3.50.

This is an autobiography of a physician who went to Africa as a young doctor and remained there to study tropical diseases, compete with witch doctors, hunt big game, explore and survey where no white man had been before. From Africa, Dr. Wellman went to Europe and later to South America, finally returning to America.

A History of Tufts College Medical School. By Benjamin Spector, M.D., professor of anatomy and professor of the history of medicine, Tufts College Medical School. 8°, cloth, 414 pp., with 49 illustrations. Boston: Tufts College Medical School Alumni Association, 1943. \$5.00.

This history is fully documented and is illustrated with large number of appropriate pictures. An appendix contains photographs of the deans and the heads of the various departments of instruction, past and present, ninety-seven persons being included in this group.

1944 Daily Log for Physicians. Champaign, Illinois: Colwell Publishing Company, 1943. \$6.00.

This standard account book for physicians has been issued in its usual format for the year 1944. Of particular interest is the comparative income schedule, considered a short cut, accurate figures for income-tax purposes. The 1944 edition also contains a new form for nonprofessional deductions—that is deductible expenses that are personal in origin and should not be included in professional expenses.

A Surgeon's World: An autobiography. By Max Thore M.D. 8°, cloth, 410 pp. Philadelphia: J. B. Lippincott Company, 1943. \$3.75.

This is the autobiography of a successful surgeon who grew up in the Old World and made his mark in Chicago.

NOTICES

ASSOCIATION OF MILITARY SURGEONS

A meeting of the Association of Military Surgeons of the United States will be held at the Waldorf-Astoria Hotel, New York City, November 2 to 4. In addition to the Surgeons General of the Army, Navy, and United States Public Health Service and by other distinguished guests there will be formal papers, panel discussions and scientific and technical exhibits on the latest advances in military medicine.

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THE MANAGEMENT OF A BLOOD BANK AT THE MASSACHUSETTS MEMORIAL HOSPITALS: THE NEW PROBLEM OF RH TYPING*

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BOSTON

IN 1938, the Massachusetts Memorial Hospitals established the first blood bank in Greater Boston. The great efficiency of this new procedure in providing blood for transfusions has resulted in its continued growth and development. In 1939 the use of placental blood for transfusions was reported.¹ In 1941 the methods followed in developing a blood bank in a large metropolitan hospital were given in detail² and a simplified citrate-dextrose blood preservative was described.³ In this article I wish to report the further progress of this blood bank in dealing with the new developments in blood typing, with special emphasis on the importance of Rh typing of all donors and recipients in the bank.

The Transfusion Service at Massachusetts Memorial Hospitals not only concerns itself with furnishing blood and plasma but is also responsible for determining the causes of transfusion reactions. In 1941 several reactions were encountered that could not be explained. Rechecking of the bloods of the recipients and donors failed to show any agglutination. By typing for the Rh factor, however, incompatibility in the blood types between recipient and donor was demonstrated and, in some cases, abnormal agglutinins were found in the patient's serum.

During 1940 and 1941, Levine,⁴ Wiener⁵ and Landsteiner⁶ published independently articles concerning hemolytic transfusion reactions encountered from the use of homologous blood that seemed to bear directly on our problem. Their conclusions are familiar and will not be dwelt on in any detail, since a complete review of the subject has recently been published by Diamond⁷ and by Hooker.⁸ Levine⁴ pointed out that a fatal transfusion reaction may result from the use of apparently compatible blood without any previous warning. He showed that Rh- patients are immunized or sen-

sitized to the Rh blood factor by gestation involving one or two Rh+ infants. Levine⁴ believed that the patient is immunized against an antigen unrelated to the blood properties A and B, which is present in the blood of the fetus but lacking in the patient's own blood. The fetus inherits the factor from the father, who is Rh+. The fetal red cells, being Rh+, build up antibodies in the Rh- mother, so that the first transfusion of an Rh+ blood may result in a hemolytic reaction. Since no warning of such sensitization and the development of anti-Rh agglutinins in the patient's serum can be obtained from a clinical examination or history, the situation is fraught with danger. Wiener⁵ also pointed out that isoantibodies for Rh, unlike those for Types A and B, do not normally occur in human plasma, and that the initial transfusion of Rh+ blood into patients who do not have isoantibodies for this agglutinin is ordinarily uneventful, the transfused cells surviving and functioning in the circulation for as long as three or four months. Subsequent transfusions of Rh+ blood, however, result in increasingly severe reactions.

Realizing that a well-organized blood bank should safeguard its patients from the possibility of such reactions, we felt obligated to carry out Rh typing in an efficient and active manner. In April, 1942, therefore, the Massachusetts Memorial Hospitals became a sponsor and member of the Blood Grouping Laboratory, an organization formed for the purpose of, and equipped for, typing for the Rh factor in human blood.

Record of Reactions.

During the past year 1169 flasks of blood have been collected and 1022 transfusions have been given. The percentage of reactions encountered was 6.4 per cent. The reactions are graded as follows: mild febrile reactions (99 to 101° F.) lasting but a short time following transfusion, with or without chills; febrile reactions (102 to 103° F.), with chills but without evidence of hemolysis; and

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The next case is reported to emphasize the difficulties that may be encountered from incomplete typing. The Blood Grouping Laboratory, as already stated, was organized in April, 1942; this patient was admitted only a few days following that date. The value of Rh typing was not yet fully realized, which accounts for the following history and did more to educate the staff than any number of lectures would have done.

CASE 2. H. M., a 33-year-old woman, was admitted with the following past history of pregnancies: a 7-pound term baby in 1932; a 2-month miscarriage, with no known cause, in 1933; a 7 $\frac{3}{4}$ pound normal baby at 9 months in 1935; 3 $\frac{1}{2}$ -month miscarriage in 1936 and 1937; a 6-pound premature baby, which was alive at birth but later died of anemia, in 1939; and an 8-pound normal baby at 9 months in 1940.

During March, 1942, the patient reported to the Prenatal Clinic. The hemoglobin was 48 per cent and the red-cell count 4,000,000. She returned to the clinic on May 8 with a hemoglobin of 36 per cent and a red-cell count of 3,000,000. Because of this progressive anemia, she was admitted to the hospital for transfusion. She was reported as Type B and was transfused the following day with Type B blood from the blood bank, cross matching showing apparent compatibility. She immediately had a transfusion reaction, with a chill and fever. Soon after the reaction started, hemoglobinuria was noted and the patient developed jaundice. Sodium bicarbonate was administered intravenously. The original blood specimens were rechecked and were found by the usual technic to be still compatible. On May 9, the patient was found to be Rh-. Her husband was found to be Rh+. On May 10 the patient went into labor and delivered a small live baby whose size corresponded to that of an 8-month fetus. The baby developed anemia on the 4th day and was found to be Rh+, showing a slight amount of anti-Rh agglutinin. After transfusion the baby did well, and on discharge from the hospital it was gaining weight and the jaundice was clearing. The mother was given a transfusion of Rh- blood, without reaction. Her blood continually improved and she was discharged on May 23. Four anti-Rh determinations were made between May 19 and May 23. Immediately following the reaction the titer became markedly reduced, only to return to approximately its original strength on discharge. Later it subsided.

On March 29, 1943, the mother was again admitted to the hospital for surgery. Following operation it was necessary to transfuse her, and she was given Rh- blood, without reaction. The anti-Rh agglutinins present before this last transfusion completely disappeared.

The last case is reported simply to show the value of routine Rh determinations on all surgical cases that have a probability of repeated transfusions. If this patient had been unfortunate enough to have received Rh+ blood, he might have had a serious reaction with the third or fourth transfusion.

CASE 3. F. B., a 75-year-old man, was admitted to the Surgical Service on November 11, 1942, with a diagnosis of carcinoma of the stomach and prepared for a subtotal gastrectomy. Realizing that several transfusions might be required, the surgical staff had him typed and found him to belong to Group A and to be Rh-. He was given one preoperative transfusion and three postoperative transfusions with Rh- blood, without reaction.

SUMMARY

The methods employed by the Massachusetts Memorial Hospitals in dealing with the Rh factor in conjunction with its blood bank have been described.

To avoid hemolytic transfusion reactions and other untoward effects from the use of banked blood, it is pointed out that Rh typing is indicated for all surgical and medical patients when there is likelihood of repeated transfusions; for all patients with a history of previous reactions; for all patients who have received emergency transfusions without typing, before a second transfusion is given; for all obstetric cases, before admission, and all surgical deliveries; and for all babies born with jaundice and anemia.

It has been demonstrated that a practical and efficient method of carrying out Rh typing for all needed cases, especially in a hospital having an active obstetric service, is the organization of a blood-grouping laboratory, jointly sponsored by several institutions.

29 Bay State Road

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FUNCTIONAL VOMITING AS INTERPRETED BY AUSCULTATION OF THE ABDOMEN

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THE two types of vomiting, postoperative and periodic, discussed in this article rest on a functional basis. Both are frequently the result of spasm of the pylorus, with simultaneous relaxation of the fundus and inhibition of the cardia. These factors may be produced by a number of different causes, the most important being certain drugs and the condition of the nervous system. Fatigue, alcohol and dietary excesses also play a leading part.

Many physicians and surgeons fail to remember that spasm of the pylorus is the primary cause of vomiting in these functional conditions, and that acidosis and loss of fluids are the result and not the cause. Furthermore, the antispasmodic action of luminal sodium is not sufficiently appreciated, and one frequently overlooks the fact that this drug stops vomiting in the majority of such cases, usually within half an hour. No good results are obtained by giving it by mouth, since it either is vomited or fails to be absorbed. It must be given hypodermically and in fairly large doses, the first one being 5 or 6 gr. Usually one dose is enough.

If one makes a practice of listening to the abdomen of patients with functional vomiting, one finds that they are uniformly silent before any medication is given. The spasm at the pylorus seems to effect the motility of the entire bowel. Twenty minutes to half an hour after the administration of luminal sodium peristalsis begins, and almost immediately the nausea and vomiting cease.

POSTOPERATIVE VOMITING

Postoperative vomiting is of frequent occurrence. It not only may be exceedingly distressing to the patient but at times results in disaster, so far as the operation is concerned. It is more frequent in nervous, high-strung persons than in others. Its occurrence depends to a large extent on the preoperative sedative and the kind of anesthetic used. Morphine is the sedative preferred by most surgeons and the one most conducive to vomiting by its central emetic action. Many surgeons still do not realize that morphine causes, on the one hand, pyloric spasm and, on the other, hypermotility of the small intestine. The net result is an irritable bowel, which together with the shock of the operation frequently produces postoperative vomiting. If luminal sodium were always used in large doses, both preoperatively and postoperatively, the incidence of vomiting and gas pains would be reduced to a minimum. Contrary to the prevailing belief, gas pains are due to a collection of gas not in a dilated, flaccid bowel but in a hypertonic and spastic small intestine. Morphine and other stimulants of the motor function of the bowel, although they

may produce a temporary relief, in the end aggravate and prolong the trouble.

Illustrative of the type of case under discussion is the following.

A 50-year-old woman had a hysterectomy and vaginal repair and was given $\frac{1}{4}$ gr. of morphine preoperatively. The anesthetic was ether. The operation was uneventful. After coming out of the anesthetic the patient vomited and continued to do so for the next 24 hours. During that time, 3000 cc. of 5 per cent glucose solution was administered intravenously and $\frac{1}{2}$ gr. of pantopon was given at 4-hour intervals, but the nausea and vomiting continued unabated. Oxygen was administered, but it had only a temporary beneficial effect. On the evening of the day following the operation, I was called to see the patient. Except for the intense nausea and vomiting, she seemed to be in good condition. The temperature, pulse and respirations were practically normal. The abdomen was not distended and was completely silent on auscultation.

With the permission of the surgeon who had performed the operation, 5 gr. of luminal sodium was given intramuscularly. No other medication was administered. Twenty minutes later the first peristaltic sounds were heard, and 5 minutes after that the patient felt better. The nausea stopped and there was no further vomiting. One half-hour following the administration of the luminal sodium she asked for something to eat.

There is nothing unusual about this case, except that the nausea and vomiting were intense and prolonged. Countless other similar cases are due to the same causes — the shock of the operation, the anesthetic and the administration of morphine or pantopon or any one of these. Having listened to the abdomen of many such patients, I believe that the chief cause is a spasm of the pylorus, which permits no gas or contents to pass from the stomach into the intestine. The evidence for this point of view is that no peristaltic sounds are heard so long as nausea and vomiting persist, and that after the administration of luminal sodium, usually twenty minutes, peristaltic sounds are heard and nausea and vomiting disappear.

PERIODIC VOMITING

Periodic vomiting is a frequent condition during the first decade of life, especially in nervous, high-strung children. Adults, especially neurotic women, are also subject to it. It is in all probability a functional condition. It may or may not be associated with attacks of migraine and it may come at regular or irregular intervals. There is apt to be more regularity in the periodic vomiting of children than in that of adults.

The apparent cause of periodic vomiting is a neurotic background. The attacks, which are often precipitated by nervous tension, emotional upsets, fatigue, overindulgences in diet and overexertion, last for a few hours or a few days and then subside. The attacks are usually preceded, in

The onset is usually without much warning, often following a hard day's work or an emotional crisis. The vomiting is apt to be frequent and severe. If the stomach contents have been expelled and the stomach has been at rest for a while, any attempt to take solids or fluids is almost sure to precipitate another attack. It is useless to give medicine by mouth in these cases, since it is never retained.

Except for the abdomen, the physical examination is usually negative. The abdomen is slightly spastic and somewhat tender, owing to strain on the abdominal muscles. It is silent on auscultation and may remain so for long periods except for an occasional tinkle. There is in all probability an intense spasm of the pylorus that is transmitted over the entire length of the small intestine. So long as the spasm lasts, the vomiting continues.

The treatment for this condition varies a good deal. Excellent results have been obtained with luminal sodium given hypodermically. As much as 6 to 10 gr. every twenty-four hours may be given. It may be necessary to repeat this dosage in the second twenty-four hours, but in my experience only one patient, whose case is discussed below, failed to respond within twenty-four hours. Luminal sodium relieves spasm and slows the peristaltic rate. The following case illustrates the condition and its treatment.

A 35-year-old woman, the mother of two children, began to have attacks of periodic vomiting when she was 20 years of age, after the first child was born. For 15 years she averaged about three attacks a year, each in her opinion due to fatigue or an emotional upset. She had had repeated examinations, including several series of x-ray examinations of the stomach and intestinal tract. Nothing abnormal was found. When the attacks first began, they were extremely severe and lasted from 1 to 2 weeks. At the beginning, vomiting was frequent, occurring every half-hour or every hour, and the patient was unable to retain anything. When she attempted to take fluids of any kind, they were immediately vomited.

The last attack of vomiting occurred in October, 1941. The patient had been working hard and was extremely tired before it started. It began with the same intensity as had the other attacks. When I was called, she had been vomiting continually for 24 hours, and even turning over in bed caused vomiting. Treatment during previous attacks had consisted of gastric lavage, the intravenous administration of 5 per cent glucose solution and the hypodermic injection of a solution consisting of hyoscine, morphine and extract of cactus. On the patient's request this treatment was continued, although it was not thought that the hypodermic injections were indicated. For 3 days, no beneficial results accrued. The vomiting continued unabated, and the patient rapidly lost weight and strength.

On the 4th day, large doses of luminal sodium were given subcutaneously—4 gr. every 6 hours. This was kept up for 2 days. On the 2nd day of this treatment, the patient still vomited, but at less frequent intervals, and the return of peristalsis was noted. On the following day,—the 6th day of the attack,—she was much improved. Vomiting stopped and she was able to take fluids without nausea. Thereafter she continued to improve.

For the past 22 months, the patient has been in good health. She has been taking two $\frac{1}{2}$ -gr. tablets of luminal sodium twice a week to allay the irritability of the stomach and nervous system and to prevent a recurrence of the attacks.

Only 6 cases of cyclic vomiting in children have been studied, but these were so similar in their history, symptomatology, physical findings and response to treatment that one may be hopeful that the underlying principle in these cases will hold true in a much larger group. All 6 children were between the ages of three and eight years at the time they were seen. All were nervous, and at least one parent of each child gave evidence of nervous instability. The parents of one patient were heavy drinkers and had been for several years preceding its birth. The symptomatology was much alike in all the cases, with vomiting once or twice a month and sometimes oftener, usually precipitated by fatigue, nervous tantrums or the consumption of indigestible food. Every patient was below normal weight. During prolonged attacks, acetone was present in the urine. Marked and persistent hypermotility of the bowel was the physical finding common to all cases. One of these patients, a boy four years of age, did not improve under treatment, and it was not until a pair of large, diseased tonsils had been removed that he began to do so. For the last two years his vomiting has practically ceased.

The following case is quite typical.

A 6-year-old girl had never been in good health, and her mother could not remember when she did not have periodic attacks of vomiting. When first seen, she was a pale and asthenic child and 11 pounds underweight. She had had an attack of vomiting about once a month, occasionally at shorter intervals, that lasted about three days; each caused extreme weakness and required 2 days' rest in bed to regain strength. Physical examination was normal except for evidence of extremely active peristalsis. For the previous 3 years, the patient had been under the care of a New York pediatrician, who had unsuccessfully tried many diets.

She was first seen during an attack of vomiting. One grain of luminal sodium was given intramuscularly, and thereafter about $\frac{1}{8}$ gr. of luminal sodium was given by mouth three times a day for 3 days. The dose was then reduced to $\frac{1}{4}$ gr. This was continued for a week and at intervals during the next 6 months. On only a few occasions since then has she had any of the drug. She has now had no attacks for 3 years, except one following "grippe." Up to a year ago, she had gained 15 pounds in weight, was going to school, played games and was apparently a normal child.

SUMMARY

Functional postoperative vomiting and periodic vomiting are in all probability largely due to spasm of the pylorus. So long as the vomiting continues, the abdomen remains silent. A few peristaltic sounds are sometimes heard at intervals.

Luminal sodium given hypodermically in large doses relieves the spasm and almost always stops vomiting. Peristaltic sounds are usually heard within half an hour after its first administration.

PRACTICAL DETAILS IN THE MANAGEMENT OF STERILITY, WITH SPECIAL REFERENCE TO ENDOCRINE FACTORS*

SAMUEL R. MEAKER, M.D.,† CHARLES H. LAWRENCE, M.D.,‡ AND SAMUEL N. VOSE, M.D.§

BOSTON

THE emotional tension of wartime and the accompanying social and economic upheavals promptly reflect themselves in outworkings of the reproductive instinct. Thus are created new and larger problems of prostitution, venereal disease and illegitimacy. Thus also new demographic trends appear, notably affecting marriage, divorce and the birth rate. In 1942 this country attained an all-time record of 3,000,000 births, the highest peak of the curve coming ten months after Pearl Harbor. At the same time there has been a great increase in the number of patients seeking the relief of barrenness. It therefore seems opportune to survey the present status of the investigation and treatment of involuntary sterility, and to define those lines of procedure that have proved to be most useful in clinical practice.

CAUSATION OF STERILITY

In order to obtain the best results in the management of sterility, one must appreciate clearly the general principles of causation, which are three in number.¹ First, clinical cases of sterility are due almost without exception to multiple causes. The average such mating presents four or five demonstrable factors of infertility. In a minority of cases some one factor predominates, in the sense that it is serious enough by itself to prevent conception. Oftener the causative mechanism is a combined action of several milder factors, each of which lowers fertility to some extent and all of which together produce a sterility that is relative rather than absolute. Second, in more than 80 per cent of cases these multiple factors are divided between the husband and the wife. Thus, it is comparatively uncommon to find that the fault lies entirely with one partner. In the aggregate, the sum totals of male and female responsibility are about equal. Third, constitutional disorders, both endocrine and non-endocrine, play a large part in the causation of human infertility. In the male they are considerably more important than are local abnormalities of the genital organs.

DIAGNOSTIC STUDY OF STERILE MATING

From what has been said about etiology, it follows that every sterility problem ought to be surveyed

from four viewpoints — urologic, gynecologic, medical and endocrinologic.¶ A basic routine should be followed, with supplementary examinations made on special indication. Complete study is essential to reveal all the causative factors present and so to permit a therapeutic attack from all possible angles. Procedure on this basis has more than doubled the number of successful results obtained. It would be sadly inadequate in sterility cases to accept the first abnormality discovered as the sole and only cause, on the unwarranted assumption that other faults do not coexist.

UROLOGIC MANAGEMENT

The urologist takes a history and makes a careful examination of the male reproductive organs. In a small number of cases these steps in the investigation reveal major obstacles to fertility, such as impotence, testicular atrophy and blockade in the epididymides. Oftener the examiner discovers conditions of comparatively minor importance. The most frequent finding is chronic prostatovesiculitis. This disorder was formerly considered to be a leading cause of male sterility because of the fact that the spermatozoa, after leaving the testicles, come into contact with bacteria and pus. Our experience has been that prostatovesiculitis, like any other chronic focal infection, contributes to infertility principally by elaborating toxins that pass into the blood stream and depress spermatogenesis.

In complete azoöspemia, fortunately comparatively uncommon, it becomes necessary to distinguish between inactivity of the seminiferous tubules and bilateral obstruction of the epididymides. Puncture and aspiration of the testicle have been used to make this differential diagnosis. A better method is testicular biopsy, which gives precise information about the functional condition of the germinal epithelium. If adequate spermatogenesis is found to be going on and if spermatozoa are present in the epididymides, the operator may proceed to perform an epididymovasostomy. Although this operation succeeds in only a minority of cases, it offers the only chance of remedying an otherwise hopeless situation.

The critical examination of semen has contributed more to the successful management of sterility than has any other detail of modern progress. With cer-

*Read at the annual meeting of the Essex North District Medical Society on May 10, 1943.

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¶In 1927 we organized the first systematic group study of sterility with the collaboration of the late Dr. A. W. Rowe. The data which is originally used by us are reported in "The last ten years experience has shown that the testis can be mutilated from the practical utility of certain of its functions in endocrinology have and therapeutic approaches."

tain reservations, it may be assumed that a quantitative estimate of male fertility is afforded by the mathematical evaluation of the spermatozoa on the four counts of number, morphology, motility and endurance. An average normal specimen contains 100,000,000 spermatozoa per cubic centimeter; 80 per cent of these are mature and well formed; 75 per cent exhibit lively motility; and under favorable conditions of temperature and moisture they remain active for the better part of twenty-four hours. If a specimen falls notably short of these standards in any respect, some degree of infertility is indicated. An excess of morphologic faults is a finding of the greatest significance, since it strongly suggests a constitutional disorder. Unfortunately, only a minority of urologists make a practice of evaluating seminal morphology, and in consequence innumerable cases of male infertility go unrecognized. This point is so important that it deserves illustration.

CASE 1. Mr. and Mrs. A had been married for 6 years and involuntarily sterile for 5. The wife presented no serious obstacle to fertility. The husband's semen showed a sperm count of 60,000,000, with 32 per cent abnormal forms, a motility of 70 per cent and an endurance of 10 hours. There was nothing grossly wrong with his genital organs. He was referred back to his family physician with the recommendation that he be further studied from the medical and endocrinologic viewpoints. The physician elected to send him to a urologist, a man eminent in his field but without special experience in sterility. The consultant reported that the patient was free from prostatovesiculitis, that his semen contained large numbers of active spermatozoa and that he might therefore be regarded as perfectly fertile. This opinion prevailed. The wife was subjected to a useless curettage, and is now, I believe, receiving vitamin E. She has not conceived nor, unhappily, is she likely to do so.

By way of contrast, a case is cited in which a similar problem was handled intelligently.

CASE 2. Mr. and Mrs. B had been married and involuntarily sterile for 3 years. By a former marriage the husband had a son 8 years old. The referring physician reported that the wife's uterus was retroflexed and contained a fibromyoma as large as a hen's egg and that the husband's semen appeared excellent. A complete investigation of the couple was carried out. Insufflation of gas showed the tubes to be patent, and postcoital examination demonstrated that spermatozoa had reached the cervix; thus both of the uterine conditions were proved unimportant as factors of infertility. The semen had a sperm count of 72,000,000, with 34 per cent abnormal forms, a motility of 75 per cent and an endurance of 24 hours. No local genital lesion was demonstrable. Constitutional study of the husband identified chronic dental infection, poor hygiene, and mild hypothyroidism. He was treated; his wife was not. The abnormal forms diminished to 23 per cent. Two months later the wife conceived, and she is now approaching the end of an uneventful pregnancy.

Pregnancy has followed improvement in seminal morphology in so many cases that one may justifiably assume a cause-and-effect relation. A detail of Case 2 worthy of emphasis is the fact that the husband, the responsible partner in this sterile mating, had been able to produce a conception nine years previously. Individual fertility levels are not constant but undergo continual fluctuations. This is easily demonstrated in male patients, in whom conspicuous changes for the better or for the worse may occur within a few months.

GYNECOLOGIC MANAGEMENT

An adequate gynecologic survey of the infertile woman includes the following items: history, abdominopelvic examination, measurement of the uterine index, study of the endocervical secretions, postcoital examination, a test of tubal patency and the taking of a specimen for endometrial biopsy.

Certain details of the gynecologic history acquire special importance when the complaint is sterility. Among these are duration of marriage, use of contraception and pregnancies, if any, with their outcome. Inquiry about the sex life sometimes reveals such infrequency of intercourse that on this count alone the chances of conception would be small. Normal menstrual behavior usually means that ovulation occurs, although exceptions are not uncommon; abnormalities are worthy of close attention as possible indications of ovarian malfunction. Perhaps a third of observant women report periodic midmenstrual phenomena, such as brief spotting, leukorrhea and *Mittelschmerz*; these symptoms presumably coincide with ovulation. Information should be obtained about previous investigation and treatment for sterility, as well as about pelvic and abdominal operations of any sort. Two recent patients took treatment for years in the hope of conceiving, unaware of the fact that they had undergone bilateral salpingectomy.

Positive findings on abdominopelvic examination must be specially evaluated with regard to their effect on fertility. Many gross lesions, notably the majority of uncomplicated retrodisplacements of the uterus, are unimportant from this point of view. On the other hand, conditions ordinarily trivial, sometimes become highly significant in sterility cases. Chronic Skene's adenitis indicates old gonorrhea, with the ever-present possibility of tubal occlusion. Stenosis of the external os and strictures of the cervix may prevent free drainage of the endocervical secretions. Stigmas of hypoplasia are often in evidence, particularly in the form of a cervix that is long, conical and anteflexed. Polycystic ovaries represent the result of faulty ovulation in the past and at the same time offer an impediment to normal ovulation in the future.

Some years ago, one of us (S. R. M.³) defined the uterine index, a quantitative measure of the differential development of the uterus based on the relative lengths of corpus and cervix. In a completely infantile uterus the index is 0.25; in the mature organ it is 0.75 or higher. True infantilism is rare, although many practitioners have the habit of making this diagnosis whenever the uterus seems small; but lesser degrees of female genital hypoplasia frequently present themselves, and are clinically important because of the fact that underdeveloped ovaries produce few if any highly fertile ova.

The endocervical mucus must afford an environment favorable to spermatozoa if they are to reach

the upper genital tract in good condition. It normally undergoes a cyclic variation in consistence, being rather thick and viscid through most of the month but becoming thinner around the time of ovulation. Congestion, inflammation and faulty drainage may lead to the formation of an inspissated mucous plug that entangles and kills the male cells. In such cases pregnancy is sometimes made possible by such simple measures as the passage of a sound, precoital clearing of the cervix and the use of heat. When the trouble is more obstinate it may require cauterization, conization with the high-frequency current or a slight plastic operation to enlarge the external os and provide freer drainage.

For postcoital examination the wife reports two hours or less after intercourse. Microscopic study of the cervical contents shows the presence or absence of spermatozoa and the condition of those present. The special value of this test lies in the information that it affords as to normal delivery and reception of the male cells. It also gives direct evidence of the favorable or harmful effect of the endocervical environment. The recovery of living spermatozoa from the cervix indicates that the husband possesses at least some degree of fertility, but does not suffice to permit the necessary quantitative evaluation. The findings of postcoital examination should always be correlated with the results of direct examination of the semen.

There are two standard methods of testing the patency of the tubes: transuterine insufflation of gas and transuterine injection of iodized oil, followed by x-ray. Each of these has its particular advantages. Insufflation gives more information about the functional condition of the tubal musculature, whereas hysterosalpingography is superior for the demonstration of structural conditions and for distinguishing unilateral from bilateral patency. It is generally good practice to do insufflation first, reserving oil injection for those cases in which the tubes are not normally patent to gas. Apparent blockades sometimes disappear when chronic passive congestion is relieved by the use of heat or when a retrodisplacement is corrected. Both insufflation and injection have therapeutic as well as diagnostic value: they are indicated in mild obstructions, in occlusions unsuitable for operation and as a detail of the aftercare of salpingostomy.

There is, unfortunately, no test that demonstrates conclusively whether ovulation has occurred. Indirect evidence may be obtained by any of half a dozen techniques, of which endometrial biopsy is the most practical. By a simple office procedure a small sample of endometrium is taken not longer than three days before the beginning of a menstrual period. If the specimen shows a normal secretory phase, one may conclude that the ovary contains an active corpus luteum, presumably the result of a recently ruptured follicle. Such a finding does not, however, prove that a highly fertile ovum has been

liberated. In cases in which the premenstrual endometrium fails to exhibit a physiologic secretory phase, there is strong reason to believe that the cycle just ending has been anovulatory.

The surgical treatment of female infertility includes procedures of three general sorts. Mention has been made of dilatation and of tracheloplasty for the purpose of improving drainage of the endocervical secretions. Operations to restore tubal patency may be undertaken with a fair hope of success, provided that cases are carefully chosen and that the aftercare is skillful.⁴ Conservative surgery of the ovaries, notably the removal of retention cysts and persistent corpora lutea, is sometimes necessary to make ovulation possible. Two other procedures should be mentioned only to be condemned. Suspension operations are irrational unless malpositions of the uterus are complicated by conditions demonstrably unfavorable to conception; they ought never to be performed except after a therapeutic trial of reposition and use of the pessary. Curettage of the endometrium as commonly practiced is not only valueless as treatment for sterility but sometimes harmful.

There is still a widespread misconception among both physicians and laymen about the indications for artificial insemination with the semen of the patient's husband. The general impression seems to be that this is a procedure of last resort, to be tried when other methods of treatment have failed. As a matter of fact, artificial insemination offers no advantage whatever over sexual intercourse in cases where spermatozoa are naturally delivered to the cervix and there encounter a favorable medium. Its utility is therefore limited to the treatment of such comparatively uncommon disorders as hypospadias, impotence, vaginismus and intractable hostility of the endocervical mucus. On the other hand, insemination with donor semen, now coming more and more into favor, provides a remedy for childlessness in that large group of matings in which the husbands are incurably sterile.

MEDICAL MANAGEMENT

Stock breeders have always found it profitable in terms of dollars and cents to pay attention to the general physical well-being of their flocks and herds. In the old days physicians made a point of giving similar care to their sterility patients. With the featuring of complicated modern techniques of investigation and treatment, this simple aspect of management has become neglected. It should receive more consideration, for the proper functioning of the gonadokinetic mechanism depends in no small measure on sound health and good hygiene.

Complete study of cases brings to light a high incidence of certain constitutional factors of infertility. One of the commonest of these is poisoning by chronic focal infection of the teeth, the nasal sinuses. Chemical poison-

example, lead and alcohol — fall into the same category. Debilitating diseases of all sorts are important, particularly the milder grades of anemia frequently encountered. Among dietary faults inadequate protein intake easily holds first place; avitaminosis is occasionally found. Sterility patients are often underexercised and in consequence suffer from the effects of a sluggish metabolism. Many of them, especially men, are victims of overwork, nervous tension and the general complex created by the artificial conditions of modern civilization.⁵

It is clinically demonstrable that disorders of the sorts just mentioned depress human fertility, sometimes severely. The practitioner who seeks and treats them as routine will accomplish not a few cures impossible by other means.

ENDOCRINOLOGIC MANAGEMENT

Physicians have come to believe that the results of endocrine treatment of infertility are generally disappointing. Many of the physiologic responses obtained in laboratory animals fail to manifest themselves with the same regularity in human beings. Optimistic claims made for new hormonal preparations prove to be exaggerated. Moreover, glandular therapy as commonly practiced in sterility cases can scarcely be expected to bring any great measure of success, since oftener than not it means simply the haphazard giving of "shots" on insufficient indications.

Although the efficacy of present-day endocrinologic methods admittedly leaves much to be desired, the fact remains that in certain types of cases the judicious use of potent glandular preparations increases fertility to the point where conception becomes possible. To accomplish such results the practitioner must have the best possible idea of the endocrinopathic states responsible for infertility and of the lines of procedure that offer a reasonable chance of correcting these disorders. He should also bear in mind that there are two important prerequisites to successful endocrine therapy. First, coexistent nonendocrine factors of infertility must be eliminated. Measures to stimulate the ovaries are obviously futile if the wife's tubes are closed or the husband has azoospermia, and yet an immense amount of treatment fully as irrational as this has been administered. Second, conditions inhibiting normal endocrine function should be removed. Under this heading come local impediments to ovulation, such as retention cysts, and in both sexes any type of depressing constitutional state, particularly toxemia from chronic focal infection.

Since the chief aim of opotherapy in sterility is to improve the production of spermatozoa or ova, it is worth while to review briefly the endocrine mechanism that controls gametogenesis. Among the several hormones supplied by the anterior lobe of the pituitary gland there are two, or possibly two phases of the same hormone, that are gonado-

tropic or gonadokinetic in the sense that they stimulate testicular and ovarian function. In the male these hormones maintain the activity both of the seminiferous tubules and of the interstitial cell of Leydig. The interstitial cells in their turn elaborate the androgenic or male sex hormone, testosterone. In the female the pituitary gonadotropic hormones bring about cyclic ripening of follicle and formation of corpora lutea. The ovarian follicle secretes the female sex hormone, estrin; the corpus luteum produces estrin and progesterone. Both testosterone and estrin have the property of limiting or checking the secretion of gonadotropins; thus a pituitary-gonad balance is established. To a certain extent this balance is dependent on the proper functioning of other endocrine glands, notably the adrenal cortex, the islands of Langerhans and the thyroid gland.

The four endocrine disorders that figure most prominently as factors of human infertility are hypogonadotropism, male hypogonadism, female hypogonadism and hypothyroidism.

Hypogonadotropism

An insufficiency of pituitary gonadotropic action during adolescence results in some degree of genital hypoplasia, with permanent anatomic stigmas and functional impairments that can seldom be corrected after the end of the plastic age. Hypogonadotropism occurring in adult patients leads to an underfunction of the testicles or ovaries that provided that these organs are essentially normal often responds to treatment.

It is not easy to make a precise diagnosis of the gonadotropic insufficiencies that usually present themselves in sterility cases. In men and non-pregnant women the urinary output of the hormones in question is so small that assays are not very helpful. Blood-serum assays may be more informative. If all other causes of poor spermatogenesis can be ruled out, such findings as oligozoospermia and defective morphology may be presumed to indicate either subnormal stimulation of the seminiferous tubules or subnormal responsiveness, both of which conditions suggest the need of a stronger gonadotropic effect. Similarly in women one arrives at a diagnosis of hypogonadotropism indirectly, on the basis of evidence of poor follicular function obtained from endometrial biopsies, pregnanediol determinations and vaginal smears. In both sexes a proper therapeutic test often serves to confirm the presumptive diagnosis.

For purposes of treatment there are available preparations of the pituitary glands of animals and anterior-pituitary-like substances of chorionic origin derived either from the urine of pregnant women or from the blood serum of pregnant mares. All these must be given parenterally, since their active principles are destroyed by trypsin. Each of them is reported to have accomplished good results in

cases of deficient spermatogenesis.⁶ As to their effect on the ovaries, they have somewhat different properties. Pituitary gonadotropins tend to ripen follicles, whereas the chorionic hormones are predominantly luteinizing. For this reason it is often advisable to use these preparations in some sort of combination. Excessive dosage should be avoided, since it may produce atresic follicles and other degenerative changes.⁷

In theory, gonadotropic therapy ought to be a specific remedy in that considerable group of cases in which deficient gametogenesis is due to pituitary underfunction. In practice, results have not come up to expectations, but successes are frequent enough to warrant the use of this method when rational indications for it are present.

Male Hypogonadism

Hypogonadism in adolescent boys interferes with the development of the secondary sex characteristics. When the secretion of testosterone drops below the normal level in adult men, other results appear. There is sometimes loss of sexual desire and potency. A more constant effect is depressed functioning of the epididymides, prostate gland and seminal vesicles.

Testosterone insufficiency may be demonstrated by absence from the urine of the degradation product androsterone. The semen is likely to be reduced in volume and to exhibit increased viscosity. The most frequent spermatozoic defects in such cases are diminished motility and short duration of life, if not complete necrospemia. Other types of poor semen, notably those with oligozoospermia and abnormal spermatozoa, are seldom if ever caused by a lack of androgenic hormones.

From the foregoing facts it follows that there are two main indications for testosterone therapy in sterility. First, androgens are valuable in impotence when this disorder is directly caused by hypogonadism. The physician should, however, bear in mind that in most cases impotence is primarily of psychic origin. Second, decreased spermatozoic vitality and thick, scanty semen indicate the need for physiologic stimulation of the epididymides and accessory glands. When androgenic treatment is undertaken it is usually advisable to give gonadotropins also, to offset the tendency of the gonadal hormones to check or inhibit the function of the anterior lobe of the pituitary gland. Without this precaution there is considerable risk of depressing spermatogenesis.

Female Hypogonadism

Inadequate secretion of estrin at the time of adolescence prevents the full development of secondary sex characteristics. In mature women a lack of estrin or progesterone, or both, produces a number of effects, in particular pathologic muscular and epithelial reactions in the tubes, uterus

The uterine disturbances may lead to abortion, as well as to various menstrual disorders, but as a factor of sterility in the sense of inability to conceive, female hypogonadism plays a relatively minor role. This endocrinopathy is a result, rather than a cause, of abnormal ovarian behavior.

Urine assays afford quantitative information concerning the excretion of the derivatives of estrin and of progesterone; in cases of the more obscure type these tests are worth the difficulty and expense entailed. Ordinarily one depends on vaginal smears to reveal estrin deficiency, and on endometrial biopsies to show insufficiency of progesterone.

The chief practical uses of estrogens in sterility, however, are not for replacement therapy in demonstrable underfunction of the ovaries, but rather for specific stimulation of the tubes and uterus. Thus, good results have been obtained in tubal obstructions, both hypoplastic and inflammatory.⁸ Thus also, whenever any marked degree of genital hypoplasia is present, a course of estrogenic treatment may advantageously precede attempts to stimulate ovulation by the administration of gonadotropins.⁹ For these purposes diethylstilbestrol and the various biologic preparations appear to be equally satisfactory. In no way, either as replacement or as stimulation, can ovarian therapy logically be expected to improve oögenesis. Nevertheless, by some mechanism imperfectly understood, cyclic estrin-progesterone treatment of certain menstrual derangements, notably amenorrhea and anovulatory bleeding, is not infrequently followed by conception.¹⁰

Hypothyroidism

It is a well-established fact that in both sexes underactivity of the thyroid gland, even of slight degree, exerts a markedly depressing effect on fertility. The mechanism may be either a secondary upset of the pituitary-gonad balance or the harmful influence of a sluggish metabolism on the germ plasm. Whatever the explanation, clinical experience proves that an adequate level of thyroid function is one of the requisites of good spermatogenesis and oögenesis.

Routine examination of infertile patients reveals a considerable incidence of hypothyroidism. Many of these patients have low metabolic rates, slow pulses and subnormal temperatures but are free from the more conspicuous signs and symptoms of their disorder. They are energetic and alert and not overweight, and in general present nothing of the typical myxedemic picture. The semen often shows oligozoospermia or a high percentage of abnormal forms.

It should be remembered that a low metabolic rate is not by itself proof of hypothyroidism, and that treatment instituted on this sole indication may be useless or even harmful. But when the diagnosis is properly established other

of infertility are ruled out, replacement therapy, with periodic checks to regulate dosage, gives remarkably satisfactory results.

SUMMARY

Some forty or fifty abnormal conditions are now recognized as obstacles to human fertility. These include constitutional depressions as well as disorders of the reproductive organs. In the typical clinical case of involuntary sterility several of these factors are present, and they are usually divided between the husband and the wife. This paper discusses the methods of complete diagnostic study prerequisite to any well-organized plan of treatment.

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BOSTON MEDICAL LIBRARY

Report of the Librarian*

THE Library passed through its second year of our participation in the war, unbombed, unwept and almost unsung. The trustees carried their burden with fortitude; the librarian made a moderate effort to use his budget appropriately; and the director and staff continued to serve the fellows and the public in the standards so long established. Slowly, as many of our more active members, the young men and women in the full bloom of their inky careers, went into the services or were called for more arduous and time-consuming hospital or teaching jobs, attendance fell off to one third and the use of our books, periodicals and pamphlets decreased by an almost equal amount, when compared with the figures for 1942. So, too, did inter-library loans. We were not actually hibernating, but our activities were somewhat slowed down in relation to the number of people we served daily. Within the Library itself, however, work went on at an even increasing pace. We tried to catch up on cataloguing and, although only 2000 new items were added to the Library in 1943, 15,000 catalogue cards were written, thus finally making available to our readers hundreds of volumes, not previously classified and catalogued. Much time was given, moreover, to our duplicate material, the director being only too glad to have a few extra moments for this important work. We were fortunate in receiving a considerable number of physicians' libraries as gifts during the year. This welcome material means to the director and his staff careful checking for items that we do not have, comparing all duplicates with our copy in order to retain the best and discard the old, classifying and cataloguing the new accessions and finally putting the items into

circulation. Thus a personal library, donated by a physician or his heirs, is integrated into our collections. In this way our library was largely built up in the past and our shelves are filled, as you well know, with the personal books formerly owned by past members. Such is the natural growth of a library such as ours, for the deeds of good men live after them in our overflowing stacks.

The rate of use of our collections remains about the same from year to year, although the quantity is less as the war proceeds. The 6000 readers of all types in 1943 used slightly more than four items apiece. Members, however, averaged eight items per individual for home use and about fifteen for use in Holmes Hall. Such figures are of little value for meticulous analysis, since many members did not use the Library at all. The estimates go to show, however, much to the satisfaction of the librarian, that the Library is used perhaps more extensively than many of our colleagues realize.

BOOK-REVIEW DEPARTMENT

The war has caused some changes in book reviews. Fewer long reviews can be published in the *New England Journal of Medicine* owing to restrictions of space, and fewer reviewers, particularly the younger men who often were actively engaged in research and the writers of books in their specialties before the war, are available. To ease the situation, an excellent compromise has been made; as each book is received, a brief description of its contents, usually limited to six or eight lines, accompanies the listing under "Books Received." In addition, certain books are selected for more extensive critical appraisal by competent reviewers, whose names are published in each index number of the semiannual volumes of the *Journal*. In 1943, seventy-eight

*Read in part at the annual meeting of the Boston Medical Library, March 7, 1944. The full report will appear in the *Sixty-Eighth Annual Report of the Boston Medical Library* (Boston, 1944).

physicians furnished one hundred and forty-six reviews. The quality of the work seems to the librarian to be uniformly good, for men chosen for this combined service to the *Journal* and the Library are among the outstanding members of the medical profession. The librarian, moreover, is fully convinced that their reviews are sounder because they are unsigned. So long as the quality of the group of reviewers is maintained, even the most sensitive author has little reason to complain of their unbiased and natural sentiments. The librarian has yet to see a grossly unfair or overpersonal book review in the *Journal*. He only wishes more reviewers would add punch to their blows! There are far too much slipshod writing, inconsequential changes to make a "new edition," and poor publishing in medical literature.

Occasionally a book is reviewed in the editorial columns of the *Journal*, particularly contributions of local interest or of outstanding value as distinctive additions to medical advancement. Three such books were so treated in 1943: the splendid book *The Embryological Treatises of Hieronymus Fabricius*, translated and edited by Howard B. Adelman, of Cornell; F. C. Irving's *Safe Deliverance*, a sound history of the Boston Lying-in Hospital and the growth of obstetrics in Boston; and Nurse Redmond's *I Served on Bataan*, a stirring account of her experiences.

SPECIAL ACCESSIONS

With book funds limited to specific purposes, the addition of books in certain fields of medicine continues to be one of the main functions of the Library. To spend such funds wisely and well is not by any means an easy task, but paths well laid down by our predecessors are usually followed in the fields of incunabula, early English imprints, Americana and books in Hebrew.

Incunabula

Twelve incunabula were added in 1943, ten after the *Catalogue* was compiled. Thus the total number of incunabula of medical and scientific interest in the Library at the end of 1943 was six hundred and eighty-four, representing the most complete collection of its type in America. With the publication of Mr. Ballard's *Catalogue*, dated 1944 but not including all accessions in 1943, it is presumed that the collection will become more widely known by scholars and consequently more useful to them. The additions, moreover, in 1943 have helped to fill out certain sections of the collection, thus carrying out our aim to make the incunabula on our shelves as representative as possible, without duplicating other holdings in Boston and its immediate vicinity. Along this line it may be noted that the addition of *De urinis et pulsibus* by Aegidius Corboliensis, according to the Stillwell *Census*, brings the first

copy of this book to New England. Three more books, or editions, of the prolific writer Philippus Beroaldus bring our total of volumes by this author up to eighteen. The Library has added another example of the *Lunarium* of Bernardus de Granollachs and now possesses three editions of this rare book, two in Latin and one in Italian. The *De lamiis et phitonibus mulieribus* by Molitoris is another book not previously listed as in New England. Still in line with the same policy is the acquisition of the *Expositio in libros posteriorum* by Thomas de Aquino, for by consulting Stillwell we find three other copies distributed in the United States, in San Marino, California, Chicago and Baltimore. With the addition of one in Boston, the regional distribution for scholars appears to be excellent. Finally, a book by Trithemius not previously represented in our collection is the only copy, according to Stillwell, in a library on the East Coast. Thus, in buying incunabula in 1943, the geographical availability of these rare books has been given due consideration in its proper relation to all the other factors that go into wise selection.

Mr. Ballard's *A Catalogue of the Medieval and Renaissance Manuscripts and Incunabula in the Boston Medical Library*, finished by February, 1943, could not be printed until the last of the year owing to war conditions, and therefore was not published until 1944. In spite of the complicated nature of the task of compiling this book, only one important error has been noted. The illustration of a manuscript in Hebrew by Bernard of Gordon (Fig. 3, page 11) was inadvertently printed upside down. This annoying oversight is not fully accounted for, but one fact in explanation, although not excusing our carelessness, is of interest. The manuscript, formerly in the Prince Dietrichstein library, was also inserted upside down by the original binder of the volume, apparently unnoticed by the Prince's librarian! A new plate, with the illustration in correct position, has been printed and distributed to subscribers of the *Catalogue* and inserted in copies for future sale.

English Imprints before 1640

Two valuable and important imprints in this class were added in 1943: the first English surgery, *The Noble Experience of the Vertuous Handy Warke of Surgeri*, by Hieronymus Brunschwig, printed in Southwarke by Peter Treveris in 1525, and *The Grete Herball*, issued the next year by the same printer from the same section of London. These two books, with two others previously acquired, *The Vertuose Boke of Distyllacyon* and *The Judycyall of Uryns*, bring to the Library examples of the four important folio publications of medical interest issued in the early sixteenth century in English. They serve to illustrate the character of early Tudor medicine at a time when medieval medicine was still holding sway though beginning

to loosen its grip before the overwhelming might of the humanistic and scientific Renaissance.

Brunschwig, an Alsatian field surgeon, who wrote a detailed account of gunshot wounds, was the author of a famous work on surgery, written in the Strassburg dialect and published in Strassburg in 1497.

lieve that he was a scholarly observer who drew many valid conclusions from his practical surgery on the field of battle. The striking illustration on the title page of the man being trephined for a head wound shows marked powers of observation. The right facial paralysis is well shown; it is clearly of

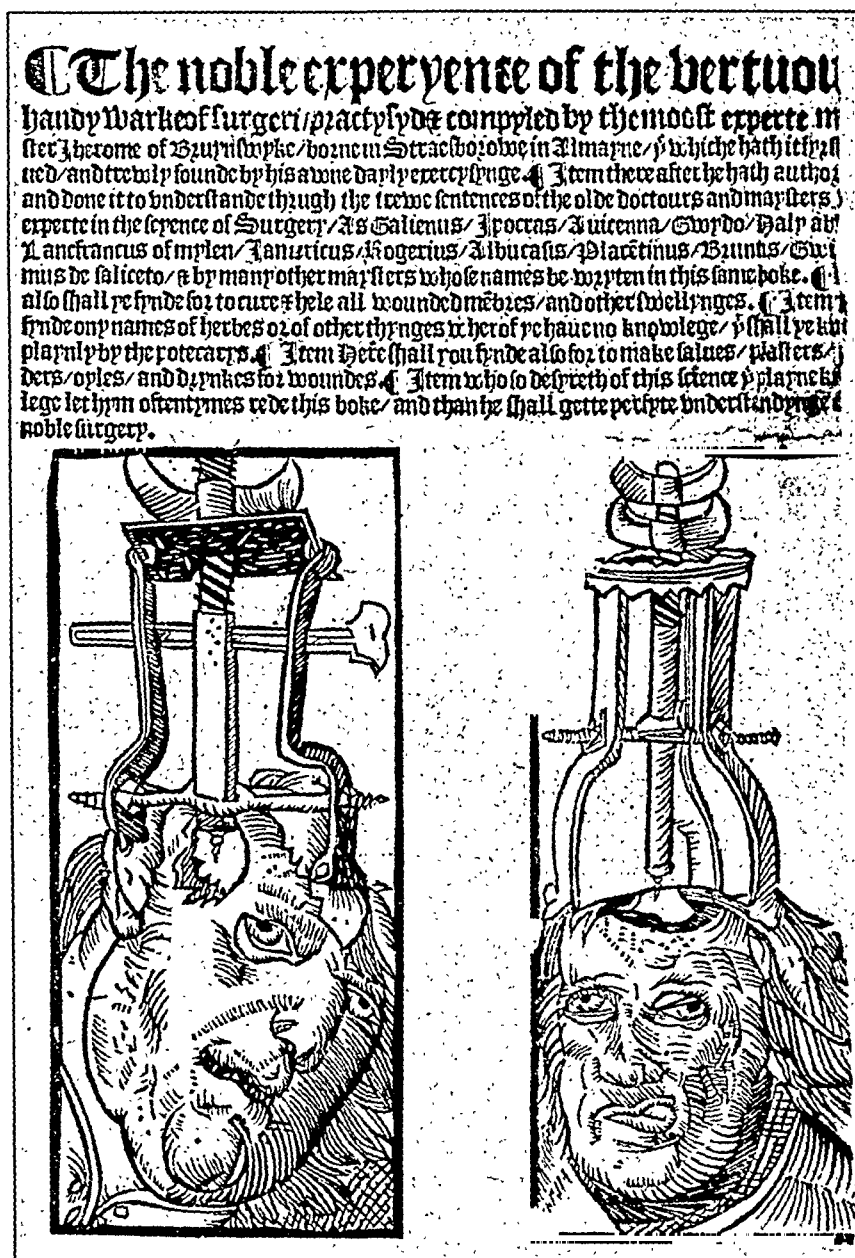


FIGURE 1. The Title-Page of Brunschwig's Surgeri (London in Southwarke, 1525).

The book was popular and full of striking illustrations. The English translation of Brunschwig's *Surgeri* (Fig. 1), printed in 1525, omits much of the text and many of the woodcuts, but still preserves the essence of the work with the description of ligature of vessels and reduction and immobilization of fractures. Although Jerome of Brunswick has not been awarded a high place in medical history, a careful reading of this book leads one to be-

the peripheral type, with the wide palpebral fissure and smooth brow. A third nerve palsy is shown on the other side, the eye being pulled to the outer corner by the unopposed action of the sixth nerve, with the dilated pupil, the result of unrestrained sympathetic stimulation. A paralysis of the left side of the tongue is also well shown. This drawing resulted from more than a hasty glance by the surgeon. The book, moreover, contains much good

advice to students and young surgeons and was certainly worthy of the folio volume provided by Treveris. One only wishes that the whole of the book with all the illustrations had been included in the first important surgery to appear in England.

The second book, *The Grete Herball* (Fig. 2), was translated from the French by Peter Treveris, the

by Treveris became the most famous of the early English herbals. It was preceded in England by only one other herbal, issued by Richard Banckes in 1525, recently published in facsimile from the rare copy in the British Museum. ¹

An important part of herbal medicine was the preparation of the herbs by distillation. To Hierony-



FIGURE 2. The Title-Page of The Grete Herball (London in Southwarke, 1526).

printer of Brunschwig's *Surgeri*, and issued from his press in Southwarke in 1526. Its predecessor, *Le grant herbier*, was one of the many fifteenth-century French herbals, dealing with medicinal plants and the virtues of herbs as remedies used in the treatment of disease. This was one of the most popular of the early herbals, compiled from sources going back into the Middle Ages. The book printed

mus Brunschwig, the surgeon, we also turn for the most complete treatise of the time. This, *The Vertuose Boke of Distyllacyon* (Fig. 3), was published by Laurens Andrewe in London in 1527. It describes the elaborate apparatus used in the technical procedure of preparing herbs.

The fourth book deals with a study of urine, one of the most valuable aids to diagnosis known to the

sixteenth-century physician. Urinalysis was developed to such an extent that often the physician made the diagnosis without ever seeing the patient. The book was also to be used by the patient so that he could properly describe the urine to his physician.

America (Boston, 1749–1751), in two volumes, by William Douglass, the writer of the controversial pamphlets against Zabdiel Boylston, has long been a desired item. Benjamin Rush's *An Account of the Sugar Maple-tree* (Philadelphia, 1792) is a wel-

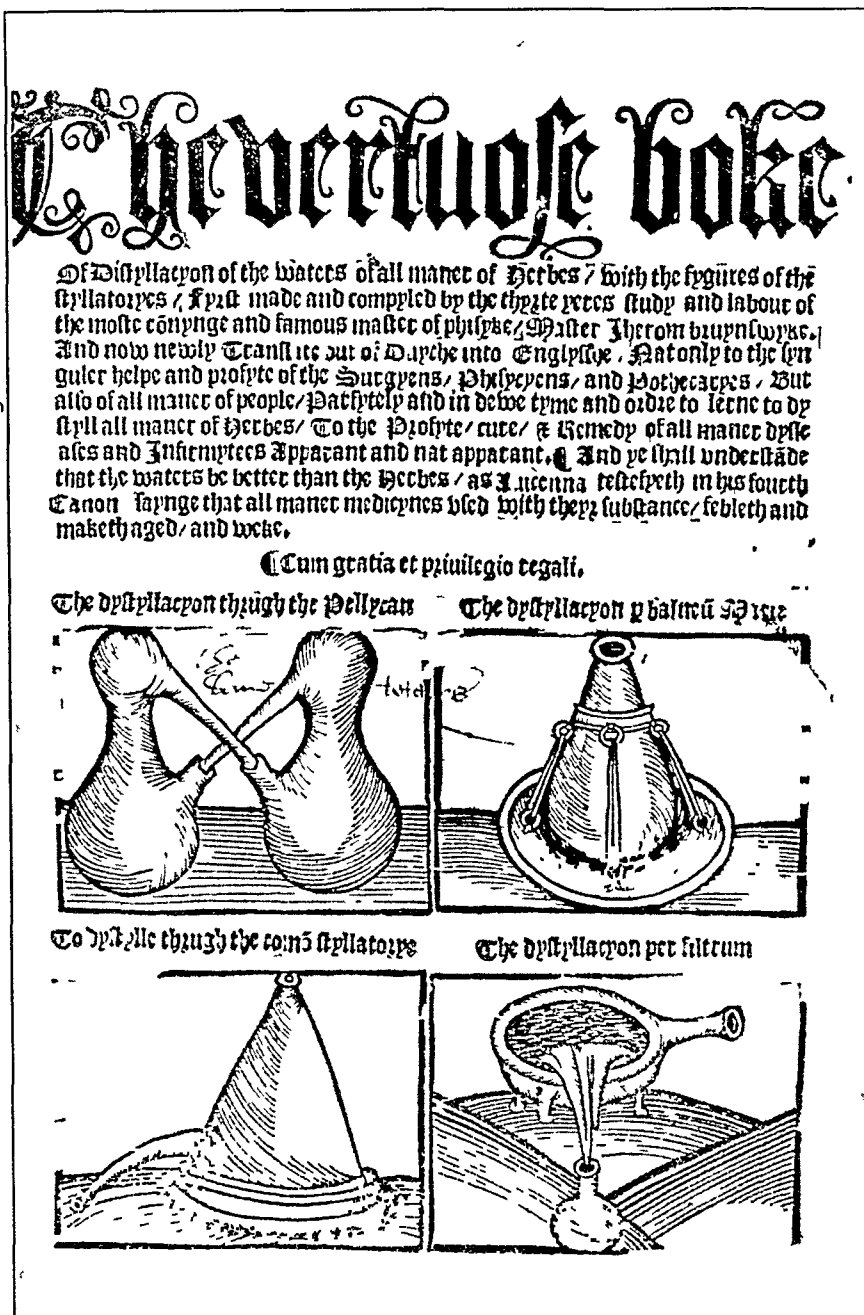


FIGURE 3. The Title-Page of Brunschwig's *The Vertuose Boke of Distyllacyon* (London, 1527).

The folio, *The Judycyall of Uryns* (Fig. 4), was published by Peter Treveris about 1527.

American Imprints

To the books published in this country we have added a few important items. The first edition of *A Summary, Historical and Political, of the First Planting . . . of the British Settlements in North*

come addition, as is the personal copy, with corrections, of *The Young Stethoscopist* (New York, 1848) by Henry I. Bowditch. The Library, moreover, has also acquired the first issue of the *Art Anatomy* of William Rimmer, published in Boston in 1877.

Other Accessions

The Library added in 1943 the daybooks of Silas Brown, of North Wilmington (1809–1844), the

prescription books from Lemon Drug Store, Marblehead (1830-1870); a considerable collection of various foreign imprints, including Linacre's translation of Galen's *De pulsuum usu*, many medical dissertations from the College of Physicians, Phila-

quarterd in our building. In addition, a rearrangement of space has allowed for a further expansion of the ever-increasing activities of the Massachusetts Medical Society, long a close associate and ardent supporter of the Boston Medical Library. With

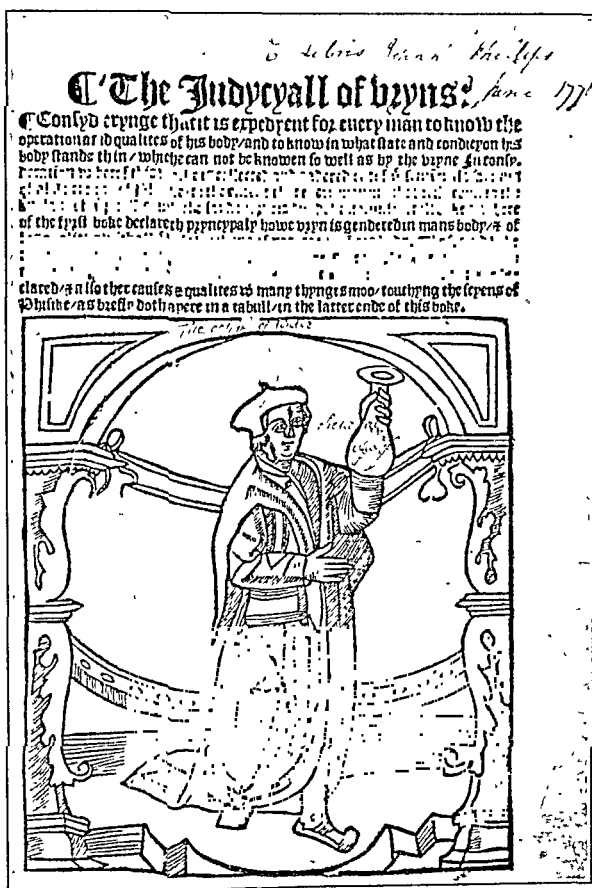


FIGURE 4. The Title-Page of *The Judycyall of Uryns* (London, 1527?).

delphia, and the University of Rochester; and numerous other gifts or purchases.

* * *

The Library continues to enjoy its close association with *The New England Journal of Medicine* and *The Journal of Bone and Joint Surgery*, both

these friends and others, together with the loyal work of the trustees and the various committees, the librarian looks back on 1943 as a successful year in medical library history and toward a fuller stage of usefulness to the medical profession and to the public in the years to come.

HENRY R. VIETS, Librarian

tions in susceptibility to this solvent dependent on age. In his series, 277 employees were studied — 158 men and 119 women. Under the conditions of exposure to tetrachlorethane experienced by this group, striking hepatic involvement was noted, and enlargement of the liver was found in nearly 25 per cent of the women but in only 12.6 per cent of the men. Not only was there a great difference in susceptibility based on sex, but it also appeared evident that older persons were much more liable to hepatic damage than younger ones. Of workers under the age of thirty, 9.8 per cent had demonstrable liver enlargement; of those between the ages of thirty-one and fifty, 29.4 per cent showed a similar finding; and in those from fifty-one to seventy years, essentially the same percentage was involved (28.5 per cent). It seems obvious, therefore, that employees exposed to tetrachlorethane should be chosen from young men. Frequent physical examinations are desirable, with particular attention to the size of the liver. Simple laboratory procedures also are indicated at periodic intervals, and determination of the level of the bile pigments in the blood and urine has diagnostic and prognostic value. In some cases in this series, hyperbilirubinemia or the appearance of bile in the urine was the first indication of liver damage. The cephalin flocculation test seemed to give additional valuable evidence.

In view of the widespread use of carbon tetrachloride in industry as well as therapeutically, a case report of acute poisoning following the accidental ingestion of between 30 and 40 cc. of this substance is of interest. Beattie and his collaborators⁶ successfully treated such a case, which was unusual because of the large quantity of carbon tetrachloride ingested and because of the successful outcome. The maximum therapeutic dose is 4 cc., and there seemed to be no doubt that the massive dose noted above was ingested and absorbed. Within nineteen hours the liver was easily palpable. Shortly afterward intensive therapy was started, consisting of the intravenous injection of a casein digest-methionine solution, at the rate of 2 cc. a minute. At the end of three hours the infusion was stopped because of chilliness, malaise and muscle aches, and it was noted that the liver was still enlarged and tender, its edge being at the level of the umbilicus. On the following day the liver was no longer tender, and its edge had receded to within 2 cm. of the costal margin. It subsequently became enlarged again, at which time the patient was treated by the oral administration of 2 gm. of methionine in the morning and evening. On the fourth day the patient was asymptomatic, and abdominal palpation revealed a second reduction in the size of the liver to near the costal margin. The subsequent course of events was entirely satisfactory. The use of *dl*-methionine in large doses in this case is of interest, and it is possible that the successful

results of treatment were primarily due to the protective effect of this amino acid.

It has long been known that many of the anesthetics commonly employed may result in transient or at times in permanent liver damage. Morrison⁷ studied the effects on liver function of seven currently used anesthetics as measured by the concentration of bile salt in the urine. Although the method employed is probably not too acceptable a measure of hepatic function, there can be little doubt that the evidence obtained by this author is reasonably accurate and suggestive. Evipal sodium, cyclopropane and nitrous oxide, under the conditions employed, showed no deleterious effect on liver function as determined by this test. Avertin and chloroform produced evidence of hepatic dysfunction lasting for twenty-four hours. Ether produced a marked disturbance in hepatic function as judged by the concentration of bile salt in surgical-drainage bile, whereas spinal anesthesia resulted in only moderate increases in elimination of bile salt. The conclusions reached in this study are in no sense new, but they are timely because of the many innovations in anesthesia that are employed at present. The chief importance of such findings should be to increase the general awareness of surgeons and anesthesiologists of the risks that may be run incident to the various types of surgical anesthesia, particularly in patients with potential hepatic damage. Because of the advantages accruing to the use of chloroform in war, it is necessary periodically to stress also its dangers. Avertin should be used with extreme caution in depleted patients and in those with biliary-tract disease, and as has been pointed out on numerous occasions, the use of ether as an anesthetic in jaundiced patients should be associated with great care and with special precautions to prevent anoxia.

The troublesome question of liver damage following the use of arsenicals has been revived because of the large number of patients receiving antisyphilitic treatment in the armed services. The hepatic pathology associated with arsenotherapy has been carefully studied by various observers. In the past, the jaundice has usually been ascribed to injury of the liver parenchyma, and in cases terminating fatally it has been possible to confirm the hepatogenic character of the jaundice by histologic studies that showed marked degenerative changes in the hepatic lobule. Hanger and Gutman⁸ in 1940 presented evidence based on liver biopsies that in some cases the icterus was the result of obstructive processes within the bile ducts rather than of injury to the liver parenchyma. In 12 cases of post-arsphenamine jaundice there was a preservation of essentially normal hepatic parenchyma, the principal lesion being pericholangitis, with bile thrombi in the finer biliary radicals. In these cases, various laboratory tests indicated little damage to

obstruction. Although the jaundice persisted for weeks or months, recovery eventually occurred. More recently Dible and McMichael,⁹ using the technic of Roholm and Iversen for obtaining biopsy material, studied 35 cases of arsenical jaundice, and in addition, cases of ordinary infectious hepatitis that were regarded as controls. These authors believed that the histologic picture and the sequence of pathologic developments in arsenical jaundice showed no significant differences from those seen in epidemic hepatitis or in the hepatitis seen after serum injections. The histologic appearance of the biopsy specimens did not support the suggestion that either syphilitic lesions of the liver or arsenobenzol poisoning played any part in their production. Although varying degrees of damage were noted, the histologic changes primarily suggested damage of the parenchymal cells.

Riddell and Anderson,¹⁰ using the oral hippuric acid test for liver function, studied a group of 188 patients already under arsenical treatment for early syphilis. Treatment consisted in the employment of neoarsphenamine or Mapharside. These authors attempted to determine whether impairment of the detoxicating function of the liver is directly proportional to the quantity of the arsenical used; whether failure of the detoxicating mechanism precedes the onset of clinical jaundice and the appearance of bile products in the urine by an interval sufficient to allow the clinician to modify the treatment; and whether the hippuric acid test is of prognostic value in postarsenical jaundice. Twenty-seven per cent of the patients receiving arsenical treatment for early syphilis excreted less than the normal amount of hippuric acid in the urine, although they were free from abnormal signs and symptoms, a finding that led the authors to believe that arsenotherapy impairs the normal detoxicating function. On the other hand, they found no direct relation between the results of the hippuric acid test of liver function and the amounts of arsenicals taken. The effect of the arsenicals on the liver, therefore, was thought to be dependent primarily on individual sensitiveness rather than on the quantity given. By means of numerous tests performed during treatment, it was shown that the failure of the detoxicating function detected in this study preceded the onset of jaundice and the appearance of bile products in the urine. Although arsenotherapy was stopped as soon as evidence was obtained of hepatic dysfunction, jaundice resulted in about one third of these cases. Tests performed every two weeks after the development of jaundice showed a steady and sometimes rapid return to normal function. A very low hippuric acid output did not necessarily imply a fatal outcome or irreparable damage to the hepatic detoxifying mechanism, a finding that should occasion little surprise.

In this regard it is of interest to refer to an article by Messinger and Hawkins¹¹ published in 1940 on

modification of arsphenamine liver injury in dogs by dietary measures. Liver injury was trivial when the animals were on a protein diet, and the damage was promptly repaired. A high-carbohydrate intake, although also beneficial, was not so highly protective as the protein diet, and on it the liver injury was sometimes somewhat greater. Progressive jaundice, severe liver injury and fatal intoxication were noted when the animals were kept on high-fat diets during the administration of arsphenamine. An interesting point, which I have confirmed in human beings, was that animals protected by high-protein or high-carbohydrate diets showed a progressive increase in the icteric index when an increase in dietary fat was given, even though no additional arsphenamine was injected. Conversely, dogs on fat-free diets that showed severe intoxication due to arsphenamine injury usually improved immediately when a shift was made to a high-protein and high-carbohydrate diet. These experimental facts are in keeping with many other investigations and are fairly well recognized, but are of special significance in relation to the care of patients who are receiving arsenotherapy for syphilis.

Of the various antisyphilitic arsenicals, Mapharsen seems to be tolerated the best. The studies of Anwyl-Davies¹² provide an interesting comparison between the results obtained after the use of neoarsphenamine and those noted following treatment with Mapharsen. Of 1946 patients treated with neoarsphenamine, the astounding number of 574 (29 per cent) developed jaundice. Of 1147 patients treated with Mapharsen, 146 (12.8 per cent) developed jaundice. Thus the latter drug not only produced less frequent evidence of hepatic damage but was also accompanied by jaundice of much shorter duration than that occasioned by other compounds, and the mortality rate was reduced. Some patients who became jaundiced after the use of neoarsphenamine tolerated Mapharsen without incident.

The possible association of infectious hepatitis (catarrhal jaundice) with arsenical jaundice has always been a moot point. For this reason the report by Mitchell¹³ is of interest. From July, 1941, to June, 1942, all soldiers in the Canadian Army in England who exhibited jaundice were hospitalized. Mitchell made a careful study of this group. A considerable number of them were found to be receiving arsenical treatment for syphilis. The clinical severity of the hepatitis encountered was relatively mild. There were no differential features between hepatitis occurring during antisyphilitic treatment and that noted in nonsyphilitic patients not receiving arsenotherapy. As suggested previously, liver biopsies showed a marked similarity of the lesions in the two groups. During the year, 0.16 per cent of the total army personnel were hospitalized for jaundice, exclusive of those suffering from extrahepatic biliary obstruction from various causes. Of these men, 17.8 per cent were syphilitic patients

receiving treatment. The remainder were nonsyphilitic patients and presumably suffered from uncomplicated infectious hepatitis. The former group represented 5.84 per cent of all syphilitic patients receiving arsenotherapy during the period. The incidence of clinical jaundice in those patients receiving arsenotherapy for syphilis was over thirty-six times as high as that in the group of syphilitic patients not receiving arsenicals. Jaundice was noted three times as frequently in the patients treated with neoarsphenamine as in those treated with Mapharsen. Deaths from acute yellow atrophy in the treated group numbered 1.47 per cent and in the untreated group 0.95 per cent. During the period reviewed, hepatitis was endemic not only in the Canadian Army in England but also in the civilian population with whom the soldiers mingled. The author suggests that a larger number of cases with infectious hepatitis without jaundice occur than has been hitherto recognized, and that it is the association of two hepatotoxic agents (arsenic and the agent of infectious hepatitis) that produces a higher incidence of infectious hepatitis in patients under arsenotherapy.

In view of recent findings in so-called "post-vaccinal jaundice," the article by Bigger¹⁴ is of interest. This author investigated the possibility that jaundice in syphilitic patients receiving intravenous arsenicals is due to the transmission of a virus from patient to patient. In the clinic under observation it was noted that the same syringe was fitted with a succession of sterile needles and was used for ten or more consecutive treatments. After each injection the syringe was thoroughly washed with sterile water and a 1:1000 solution of biniodide, five washings in all. It had been presumed that the procedure used would remove the few drops of blood drawn into the syringe at the beginning of each injection, but experiments showed that the method of cleaning the syringes was not sufficient to remove all the living organisms from it when these were present in the blood. A virus might thus pass from patient to patient in clinics where the same or similar techniques were used. Such a finding is extremely suggestive as helping to explain, at least in part, the incidence of jaundice in this particular group of patients. The suggestion of the author that a thoroughly boiled syringe be used for each patient is obviously sound.

Rossling¹⁵ studied the effect of arsenic on the liver in relation to acute and chronic forms of damage. From a variety of observations, he concluded that cirrhosis of the Laennec type due to arsenical poisoning alone is unlikely, and stresses the importance of considering the additive effects of such substances as alcohol, lead, nicotine and copper and those of infections, metabolic disturbances and cachexia. Certainly the combination of hepatic infection and malnutrition may well form the background for specific toxic damage to the

liver when the dosage of the poison is minimal. The summation effect of several factors in producing liver damage is also mentioned by Kulchár and Reynolds¹⁶ in a discussion of bismuth hepatitis. Although it can hardly be stated that liver damage from bismuth is a generally accepted fact, the survey of 120 cases made by these authors is of considerable interest. Jaundice developed in this group of patients during courses of bismuth therapy for syphilis. Except for 2 patients, all were in the latent stage of the disease. Half the entire group had received varying amounts of treatment prior to entry, but none of these patients gave a history of previous jaundice. In over 8 per cent of the patients treated, there was a recurrence of hepatitis with a resumption of bismuth therapy. The effect of previous arsenical therapy, as well as the less evident factors of diet, alcohol and intercurrent infection, was thought to have predisposed the liver to damage from bismuth.

Reports on hepatic damage following sulfonamide therapy have been occasionally presented. In most, if not all, cases such damage has appeared to be the result of an individual hypersensitivity or an organ hypersensitivity rather than of overdosage. The observations of Machella and Higgins¹⁷ are striking and worthy of comment. These authors carried out four separate experiments devised to determine the effect of sulfanilamide on the already damaged liver or on the liver predisposed to damage by a recognized procedure. The drug was administered to rats in which hepatitis had been induced by carbon tetrachloride, to a second group in which hepatitis was being induced by the same means, to a third group receiving alcohol and finally to a group in which obstructive jaundice had been induced by ligation of the common duct. In the animals in which hepatitis had already been produced by carbon tetrachloride, sulfanilamide did not increase the damage to the liver but appeared to lessen it; in the second group, the drug did not impede regeneration of the liver after the administration of carbon tetrachloride had been discontinued. In the animals receiving alcohol and sulfanilamide, no damage resulted to the hepatic cells, although in some of the animals receiving only alcohol fat was deposited in the liver. In the animals with extrahepatic biliary obstruction, no detectable injury to the liver not ascribable to the biliary obstruction was produced. On the basis of these experiments, reported in 1942, Forbes and Evans¹⁸ carried out further experiments on the protective action of sulfanilamide against hepatic damage from chloroform. These studies were made primarily because of the desirability in modern warfare of such an anesthetic, which is not inflammable and can be transported in small bulk. Acute poisoning was produced, and the animals were sacrificed twenty-four hours later. Histologic examination of the livers showed that the oral administration of

sulfanilamide apparently exerted a protective action against damage to the liver from the inhalation of chloroform in both rats and rabbits. On the basis of these experiments, the authors suggest that sulfanilamide or some other sulfonamide compound be given preoperatively to wounded men who are to be anesthetized with chloroform, and stress the wisdom of giving the drug soon enough to obtain a therapeutic level in the blood stream and liver before the administration of the anesthetic.

That sulfathiazole and sulfadiazine do not necessarily constitute a threat to hepatic efficiency in the treatment of bacterial infections is suggested by the studies of Peterson, Deutsch and Finland.¹⁹ These authors report a series of 37 patients who showed evidence of acute or chronic liver damage and who, for various reasons, received one or the other of these drugs in full therapeutic doses. Studies were made to determine the effect of the drug on hepatic function. In patients with acute hepatitis and bacterial infection, sulfonamide therapy was almost always accompanied by improvement in hepatic function paralleling improvement in the underlying infection. In patients with chronic liver damage, there was no aggravation of the hepatic condition during the administration of the drug. There was some apparent improvement in the cases in which bacterial infection was added to hepatic injury. On the other hand, severe toxic effects, other than those of direct injury to the liver, were unusually frequent in patients with portal cirrhosis and intercurrent infection. These undesirable reactions were about twice as frequent after the use of sulfathiazole as after treatment with sulfadiazine. The authors conclude that the presence of liver damage should not be construed as a contraindication to therapy with sulfathiazole or sulfadiazine in patients with bacterial infections against which these drugs are effective, sulfadiazine being the drug of choice. Caution should be exercised in the administration of sulfonamide compounds in patients with severe portal cirrhosis of the liver.

That sulfonamide therapy may occasionally result in direct damage to the liver, however, is indicated from various recent clinical reports. Menten and Andersch²⁰ report, out of approximately 300 autopsies performed during three consecutive years, 38 cases of liver disease in children who had had sulfonamide therapy. Pathologic changes included toxic necrosis of the liver in 3 patients, toxic central necrosis in 9 patients and serous hepatitis and beginning toxic central necrosis in the remainder. No relation could be established between the sulfonamide dosage and the development of liver lesions. The Gray colloidal-gold test of liver function was positive in 13 per cent of the children studied, and slightly positive in an additional 20 per cent. No correlation was found between the amount and duration of therapy and the colloidal-gold reaction. Like all recent observers,

these authors believe that inadequate nutrition may render the liver more vulnerable to the sulfonamides. They stress particularly protein depletion and an inadequate intake of vitamin B. Cantarow and Wirts²¹ mention the presence of hyperbilirubinemia following the administration of sulfonamides in an important number of cases. Twenty patients were studied, and increases of blood bilirubin were noted at periods ranging from one to seven days after the institution of sulfonamide therapy. A return to normal followed in every case after cessation of treatment. Other evidence of hepatic functional impairment was demonstrated in 2 cases treated with sulfanilamide, in 3 cases following the use of sulfathiazole, in 2 after sulfapyridine and in 3 after sulfadiazine. Hyperbilirubinemia occurred after the administration of varying amounts of the drugs and with widely varying sulfonamide concentrations in the blood. When one considers the total number of patients receiving sulfonamide therapy in one form or another without deleterious effects on hepatic function, and the paucity of cases such as those already cited, one is forced to conclude that in most cases these drugs do not cause tremendous danger to the liver, particularly when a proper indication for their employment exists. Thus, Anglem and Clute²² cite 75 cases in which intraperitoneal sulfanilamide was used following gastrointestinal resections, with a toxic reaction to the drug in only 1 case. In this case a toxic hepatitis occurred, but recovery took place.

The potential damage to the liver from the use of tannic acid in the treatment of burns has been recorded by several observers. With newer methods of treating burns, this hazard will presumably become of little or no importance. The possibility of such danger, however, should be mentioned if for no other reason than to stress the inferiority of tanning to other procedures that are less dangerous as well as more efficacious for the treatment of such common injuries. That hepatic damage may result from serious burns of large areas of the body without the addition of any chemotherapeutic factor is the assumption of Boyce.²³ This author discusses the hepatic factor in burn cases from experimental, clinical, laboratory and autopsy aspects. The article is of particular interest in relation to the unexpected fatalities that occasionally occur in slightly burned persons. It is quite possible that in these cases certain toxic factors associated with the burn exist that have produced a minimal amount of liver damage, and that additional therapeutic measures may provide the necessary factor for ultimate fatal poisoning of the liver. An autopsy report by Duffin²⁴ shows what seem to be the characteristic findings associated with tannic acid poisoning of the liver. In this case, about one twelfth of the body surface was burned, and the treatment was essentially that of tanning. Icterus developed

on the second day and progressed rapidly, with concomitant enlargement of the liver. On the eighth day, however, the jaundice had diminished and the liver was no longer palpable, but because of intercurrent pneumonia death occurred on the tenth day. An autopsy showed intense central and mid-zonal necrosis. A careful experimental study of the relation of tannic acid to liver necrosis occurring in burned patients was published in 1942 by Wells, Humphrey and Coll.²⁵ Central necrosis of the hepatic cells was noted not only in 4 patients who died following such treatment for burns but also in a large number of animals experimentally injected with tannic acid. The degree of hepatic damage in general varied directly with the amount of tannic acid injected. Further observations were made by Forbes and Evans,²⁶ who also showed that in rats tannic acid injections were hepatotoxic. These authors, moreover, found that no protection was afforded either by the oral or subcutaneous administration of sulfanilamide or by the subcutaneous administration of xanthine.

That massive burns predispose to liver damage, even in the absence of coagulating agents used in burn therapy, is indicated by the studies of Hartman and Romence.²⁷ Large experimental burns resulted in engorgement of the sinusoids of the liver, especially in the central areas. The introduction of coagulating agents — tannic acid, ferric chloride and silver nitrate — increased the incidence of degeneration and necrosis of the liver cells. Tannic acid used as a wet dressing produced clinical jaundice and central necrosis; the administration of subcutaneous tanning produced liver necrosis in 25 per cent of the animals; and when given intraperitoneally, it caused necrosis in 33 per cent. Various tannic acid preparations were employed, and similar results were obtained with each. Silver nitrate administered subcutaneously produced necrosis and edema at the site of injection and, at the same time, degeneration, hemorrhage and necrosis of the liver, but not the clinical jaundice that was observed following the use of the tannates. Ferric chloride introduced subcutaneously also produced necrosis, edema and hemorrhage at the site of inoculation, and hepatic lesions, with clinical jaundice, that resulted in death. Clark and Rossiter²⁸ obtained further information regarding the toxicity of tannic acid by following liver function in rabbits after the use of this drug. Impairment of liver function in these animals was demonstrated by intravenous galactose-tolerance tests. Barnes and Rossiter²⁹ also carried out experiments on guinea pigs and mice with tannic acid and sodium tannate that were entirely in keeping with the foregoing. After application of tannic acid to the raw area produced in guinea pigs by burns to the extent of one third of the body surface, there was slight liver damage, which was definitely greater than that seen in untreated similarly burned.

The harmful effect of other therapeutic agents on hepatic function has also attracted attention. Krupski et al.³⁰ studied the effect of caffeine on the liver in rabbits. Solutions containing several milligrams per hundred cubic centimeters did not affect the oxygen consumption of perfused rabbit livers, although higher concentrations (100 mg. per 100 cc.) increased the oxygen uptake. When the initial caffeine concentration was as high as 200 mg. per 100 cc. in the perfused blood, the final caffeine concentration after one hour or more was 17.5 per cent of the initial caffeine concentration. It is evident that the liver progressively lost the ability to destroy caffeine when the drug was administered in concentrations above 200 mg. per 100 cc.

It has been generally recognized that liver damage is accompanied by an impaired tolerance to morphine and other alkaloids. Gross³¹ carried out a study on the effect of liver damage on morphine conjugation in tolerant and nontolerant dogs maintained on a constant diet and constant water intake. Urinary morphine determinations were made before and after liver damage with the animals on a constant dose of morphine. Control observations on the damage produced by carbon tetrachloride were obtained by repeated determinations of brom-sulfalein excretion. The urine was analyzed for total, free and easily hydrolyzable morphine. The fraction of morphine that was hydrolyzable with difficulty was determined by the difference between the last two figures and the total urinary morphine. The author's earlier observation that liver damage by chloroform produced an increase in free morphine excretion also held true when carbon tetrachloride was used as the damaging agent. In addition to the marked increase in free morphine after carbon tetrachloride injury, there was a decrease in the excretion of the easily hydrolyzable fraction of combined morphine. Since the total recoverable morphine was not materially altered and the portion hydrolyzed with difficulty remained fairly constant, the easily hydrolyzable compound appeared as free morphine. One may conclude from these experiments that the easily hydrolyzable form of conjugation is the only one that takes place in the liver. Liver damage apparently inhibits the conjugation of morphine to a certain extent, as shown by the fact that the free morphine found in the urine increased without any corresponding increase in the total morphine excreted. These studies confirm and partially explain the known clinical fact that ordinary clinical doses of morphine may present special hazards when administered to patients with liver disease.

Although the exact effect of alcohol on the liver is imperfectly understood, there can be little reasonable doubt that this substance is a noxious agent in the presence of hepatic damage. It is generally accepted that the primary oxidation of alcohol

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CASE RECORDS OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

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EDITH E. PARRIS, *Assistant Editor*

CASE 30251

PRESENTATION OF CASE

A fifty-six-year-old toolroom clerk was admitted to the hospital complaining of increasing weakness. The patient had been well until a year prior to admission, at which time he noted generalized weakness becoming progressively more pronounced. This was accompanied by gradual weight loss, amounting to 25 pounds. Six months before entry he had severe diarrhea, lasting about two weeks and associated on one occasion with nausea and vomiting. This was followed by a rise in temperature (105.2°F.) and a diffuse cherry-red erythema over the upper portion of the body. This episode lasted for about three days, the temperature gradually reaching normal. Following it, weakness was more pronounced, and weight loss more rapid.

Because of these symptoms he attended a local outpatient department, where he was found to have anemia (2,500,000 red cells, with 7 per cent reticulocytes). The spleen, but not the liver, was palpable. The urine showed a +++ test for albumin, with rare hyaline casts. The stomach content contained no free hydrochloric acid, and was positive for occult blood and lactic acid. Treatment with Feosol, yeast and dilute hydrochloric acid resulted in little improvement and three months later he was finally admitted to a local hospital, where he remained for five weeks. At that time the liver was palpable five fingerbreadths below the

costal margin; the spleen was still palpable. The red-cell count was 2,750,000, with 10.5 gm. of hemoglobin; the mean corpuscular volume was 109 cubic microns, the mean corpuscular hemoglobin 38 millimicrograms, and the reticulocyte count 0.4 to 2 per cent. The bleeding, clotting and prothrombin times were normal. The icteric index was within normal range. The serum protein was 8.7 gm. per 100 cc., with an albumin-globulin ratio of 2. The serum phosphatase was 13 Bodansky units per 100 cc. X-ray studies of the chest, gastrointestinal tract, long bones and pelvis were negative. A sternal marrow biopsy revealed no characteristic cellular picture, but suggested pernicious anemia. A liver biopsy revealed almost complete replacement of normal tissue cells by dense fibrous tissue in which there was bile-duct proliferation. The liver on peritoneoscopy appeared grossly enlarged and roughly granular.

Following discharge, the patient was treated with yeast and liver by mouth and parenterally, with no response, and he was finally admitted to this hospital two months later.

Physical examination revealed a pale man, showing evidence of recent weight loss. A spider angioma was present on the neck. An area of diminished resonance and inconstant inspiratory rales was present at the right base. The heart revealed a soft systolic murmur, not transmitted, over the pulmonary area. The liver edge extended from the right iliac crest to the costal margin in the left mid-clavicular line and felt somewhat nodular. The lower pole of the spleen was palpable. The prostate was slightly enlarged. There was questionable pitting edema of the ankles.

The blood pressure was 100 systolic, 60 diastolic. The temperature was 99.2°F., the pulse 80, and the respirations 20.

Examination of the blood revealed a red-cell count of 2,570,000, with 8.5 gm. of hemoglobin. The white-cell count was 5700, with 49 per cent neutrophils, 30 per cent lymphocytes, 20 per cent monocytes and 1 per cent eosinophils. There were a few macrocytic red cells. The urine revealed a +++

*On leave of absence.

test for albumin, and occasional red cells, white cells and granular casts. A bromsulfalein test showed 30 per cent dye retention. The van den Bergh was within normal limits. The protein ranged from 6.2 to 7.0 gm. per 100 cc., with an albumin-globulin ratio of 2.1 to 2.5. The blood cholesterol was 122 mg. per 100 cc., the calcium 10.7 mg., and the phosphorus 4.8 mg. The alkaline phosphatase was 4.8 units, and the acid phosphatase 1.8 units per 100 cc. A Congo red test was negative for amyloid. The prothrombin time was 22 seconds (normal, 16 seconds). A blood Hinton test was negative.

A roentgenographic examination of the chest, a gastrointestinal series and a barium enema revealed no abnormalities, except an enlarged liver and spleen.

On the sixteenth hospital day a peritoneoscopy revealed an enlarged liver, exactly as palpated, with a tongue of liver tissue extending down below the umbilicus in the right lower quadrant and flank. The surface was mottled, reddish-yellow and questionably granular; there was a fairly sharp edge. There was no evidence of neoplastic implants. The spleen was about twice its normal size, smooth and dark brown. There was no ascites. The liver was biopsied.

DIFFERENTIAL DIAGNOSIS

DR. CHESTER S. KEEFER*: The patient was fifty-six years of age and had been ill for over a year with constitutional symptoms and loss of weight, increasing fatigability and weakness. In the past there had been one episode of diarrhea of two weeks' duration, during which time he developed a temperature of 105°F., and a diffuse cherry-red erythema over the upper part of the body. I am unable to explain that episode. It has occurred to me that perhaps this man had received some sulfonamide from one of his physicians for the treatment of diarrhea and developed the fever and skin eruption as a result. It is not stated, however, in this record whether that was known. There are few patients who have diarrhea of more than two or three days' duration who do not receive one of the sulfonamides; some of them develop fever and a skin eruption if the drug is continued for a period of seven days or longer.

One might, for the sake of mental exercise, indulge in some speculations concerning what other disorders cause diarrhea and skin eruptions. We know that certain strains of hemolytic *Staphylococcus aureus* are capable of liberating exotoxin as well as endotoxin, and occasionally these patients show a typical scarlatiniform eruption associated with infection. These infections are of short duration, the skin lesions are exfoliative in charac-

ter, and the gastrointestinal symptoms appear within a short period after the ingestion of food. The common foods that are contaminated by the staphylococcus, of course, are custard pies and the filling of cream puffs. If the organisms grow freely, they liberate an exotoxin and some strains liberate an erythrogenic toxin, which is exceptionally difficult to distinguish from the streptococcal erythrogenic toxin. Antiscarlatin antiserum will, on occasion, blanch the rash of staphylococcal infection.

When this patient was admitted to the first out-patient department he had an anemia with enlargement of the spleen and albuminuria. This anemia apparently did not respond to any form of treatment that was prescribed — iron, yeast and dilute hydrochloric acid. One might expect that the anemia would be refractory to hydrochloric acid, but not to the iron or the yeast. On admission to that hospital the anemia was still present and was hyperchromic. The sternal marrow biopsy showed nothing definite but was suggestive of pernicious anemia. The liver biopsy showed dense fibrous tissue, with bile-duct proliferation. That is the picture that one might see in extensive cirrhosis of the liver. With fibrosis, the bile ducts make a frantic effort to proliferate and to join up with the new nodules in an attempt to excrete bile from these cells. I think that we cannot accept that conclusively, however, in light of the fact that the liver increased in size rather than decreased. In any event it seems clear that this anemia was refractory and did not respond to liver, and that it was not an ordinary pernicious anemia.

The physical examination on the last admission says that a spider angioma was noted over the neck. When one finds spider angiomas it is usually suggestive that the patient has liver disease. These spider angiomas attracted attention in the medical literature over twenty-five years ago. If you read about the old descriptions of cirrhosis of the liver they are freely discussed. Then, for a long time no one paid any attention to them, but in the last few years a great deal of interest has again been shown. They are dilated arterioles, and when examined carefully, they tend to occur only on the upper half of the body and, for some curious reason, over the area drained by the superior vena cava. It has been suggested that the disturbances in the estrogenic hormones that take place in liver disease may be responsible for these angiomas. In any event it was noted here that there was a spider angioma on the neck, suggesting that the man had liver disease.

Then, once again, there were enlargement of the liver and spleen, anemia that did not respond and albuminuria. Someone expressed the opinion that this man may have had amyloid disease because of the albuminuria, the big liver and the enlarged spleen. This was a good suggestion, but the Congo

*Director, Evans Memorial, Massachusetts Memorial Hospitals; physician-in-chief, Massachusetts Memorial Hospital; and Professor of Medicine, Boston University School of Medicine.

that he retained at least 30 per cent of the dye, indicating that he had a disturbance of hepatic function.

The x-ray studies were negative except that they showed an enlarged liver. Finally, there was another peritoneoscopy, and they found that the liver was still large; a biopsy was taken, and Dr. Castleman will shortly tell you the diagnosis.

The question that arises in this patient, of course, is, Was this simply a case of cirrhosis of the liver, or was there some process superimposed on the cirrhosis? If one assumes that it was just cirrhosis, it is difficult to explain why the liver was enlarged. One must believe the record, which states that the liver increased in size from the first admission until the time of the biopsy that disclosed the answer. Patients who have an enlarging liver usually have some infiltrating process in that organ. The one type of liver disease that is associated with fibrosis, and even with cirrhosis, and a very large liver is the fatty liver. They may reach enormous proportions, weighing 4000 to 5500 gm. The story in these cases is usually characteristic. The patient is either a heavy gin or whisky drinker, consuming anywhere from a pint to a quart a day over many years. There is no evidence that this was an enlarged fatty liver.

The first examination, with the tender spleen and hyperchromic anemia, certainly suggests that he might have had pernicious anemia, but that was not borne out by the therapeutic test and did not seem to be borne out by the gradual enlargement of the liver. One may encounter a refractory form of macrocytic anemia in patients with cirrhosis of the liver or some disorder of the bone marrow, such as a lymphoma. That naturally raises the question whether this patient might have had a lymphoma with a big liver, a big spleen and an anemia that was macrocytic in type. From the original biopsy, however, there is no evidence that there was lymphocytic infiltration of the liver. The bone marrow showed no changes consistent with the diagnosis of lymphoma. So we have no basis in this record for making such a diagnosis.

It seems to me that the likeliest explanation for this case is that the patient had a cirrhosis of the liver on which was superimposed a carcinoma, but when one makes that diagnosis one is always treading on dangerous ground. There are two forms of primary liver-cell cancer. One is a hepatoma, in which there is an initial lesion that expands and usually metastasizes by way of the veins, so that there is one large lesion with multiple small or varying sized nodules in the liver, with few metastases elsewhere. The other type of liver-cell carcinoma usually arises from the small bile ducts. There is some evidence in this case that diffuse fibrosis of the liver was present, with bile-duct proliferation. That is somewhat suggestive that this proliferation of the bile ducts was not just the type that one

the liver with disorganization of the tissue. The one point that I cannot explain on the basis of uncomplicated cirrhosis of the liver is the fact that the liver was so large. We know that it was fibrous and that the liver increased in size. These are the points that lead me to suspect that this man had cirrhosis of the liver with a superimposed carcinoma of the bile-duct-cell type. That is the best diagnosis that I can offer; perhaps, in addition, the patient had some degree of nephrosclerosis.

DR. BENJAMIN CASTLEMAN: The field is still wide open.

A PHYSICIAN: The patient had diarrhea for two weeks, high fever and a large spleen. The liver increased in size so rapidly, without pain or jaundice, that one might suspect that he had either amebiasis or some other infection that was causing an abscess there.

DR. CHESTER M. JONES: It seems to me that, with an amebic abscess, the patient would have been running a septic temperature.

DR. CASTLEMAN: The chart was flat.

DR. WYMAN RICHARDSON: How about the right half of the diaphragm?

DR. LAURENCE L. ROBBINS: It is normal. About all that these x-ray films do is to confirm the findings of physical examination — an enlarged liver, which extends down over the iliac crest, and a large spleen, which is visible below the costal margin. The only thing that I can add is that there are definitely no varices of the esophagus. The diaphragm is perfectly smooth in outline and shows nothing to suggest lobulation.

DR. RICHARDSON: The bone marrow was normal?

DR. CASTLEMAN: That examination was done at another hospital. We have only the report.

Dr. Jones saw this patient and said: "I am not convinced that cirrhosis is the answer, although it may be. The lack of fever, varices and ascites and the presence of a big liver make me question the diagnosis of cirrhosis of the liver." Have you any further comment, Dr. Jones?

DR. JONES: No, except I think that the first biopsy report of fibrosis and apparent bile-duct proliferation does not prove that that was the picture throughout the liver. I do not believe that it was.

DR. CASTLEMAN: Unless a man is expert at taking a biopsy through a peritoneoscope, he may take a bit of the capsule of the liver, with little underlying tissue, so that the specimen is not a true sample of the liver.

DR. JONES: The specimen may be a thickened capsule with a few bile ducts, and thus does not give an accurate picture. I do not believe that this biopsy makes or breaks the diagnosis. If it were pure cirrhosis, it would tend to be a fatty liver, as Dr. Keefer has pointed out, or biliary cirrhosis. The description given at the second peritoneoscopy — a smooth or finely granular liver with mottled

yellow areas — is not at all unlike what we see in cases of biliary cirrhosis, but it is curious for biliary cirrhosis to show this clinical picture. It does happen, but it is unusual.

DR. CASTLEMAN: How would Dr. Keefer account for the appearance of the liver at the second peritoneoscopy with a diagnosis of cirrhosis and hepatoma? Would they not be easily visible?

DR. KEEFER: That would depend entirely on how far from the surface the hepatoma was. In some hepatomas the original mass is beneath the capsule and does not project beyond the capsule. Although many of them produce large lobulated masses of the liver, a few do not.

DR. RICHARDSON: It would be useful to have detailed information regarding the blood picture. This

CLINICAL DIAGNOSIS

Cirrhosis?
Carcinoma of liver?

DR. KEEFER'S DIAGNOSIS

Cirrhosis of liver, with superimposed bile-duct-cell carcinoma.

ANATOMICAL DIAGNOSIS

Plasma-cell myeloma involving liver and bone marrow

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The biopsy of the liver showed no evidence of cirrhosis. The most striking finding

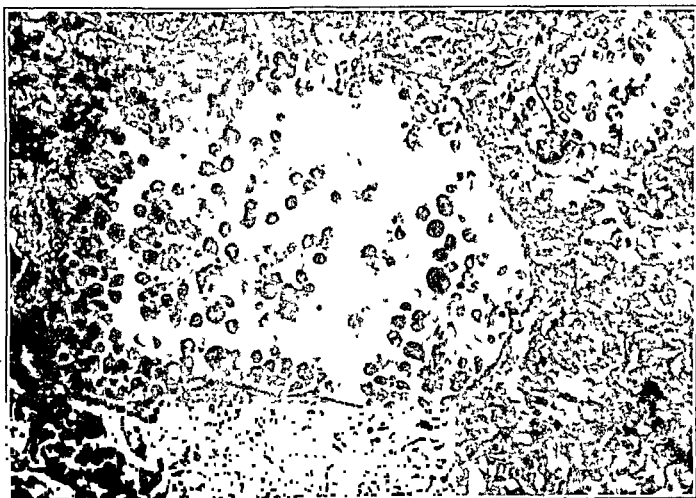


FIGURE 1. Photomicrograph of the Biopsy Specimen from the Liver.

was a macrocytic anemia. Pernicious anemia could account for it.

DR. CASTLEMAN: I do not believe that the blood picture as reported gave evidence of pernicious anemia.

DR. RICHARDSON: The mean cell volume was 109 cubic microns. I do not know where it was done. If it was done in the Baker Memorial Laboratory that would be on the macrocytic side. Ordinarily it should perhaps be more than that before one could be sure that it was really a macrocytic anemia; 120 cubic microns would be quite suggestive, 109, slightly suggestive.

DR. J. H. MEANS: I suppose it could be lymphoma, although there is no proof of it. He had a large spleen, anemia and fever on one occasion, all of which is suggestive.

was tremendous dilatation of the sinusoids, which were filled with typical plasma cells (Fig. 1). This patient, therefore, had plasma-cell myeloma involving the liver.

To confirm that diagnosis a sternal biopsy was done, and this showed that the marrow was almost completely replaced by plasma cells. When that was confirmed a peripheral blood smear was examined by Dr. Richardson, who found plenty of plasma cells.

The urine was examined and found to contain Bence-Jones protein, which had not been looked for before.

The patient died at home three months later, but no post-mortem examination was performed.

X-ray films were taken after the diagnosis was established.

count was 2,180,000, with 8.3 gm. of hemoglobin. The blood nonprotein nitrogen was 36 mg. and later 26 mg. per 100 cc., and the chloride 88.5 milliequiv. per liter. The blood protein varied from 5.8 to 7.2 gm. per 100 cc., with an albumin-globulin ratio of 0.8. A formol-gel reaction was positive (+ after five minutes, ++ after two hours and +++ after twenty-four hours). A brom-sulfalein test revealed 10 per cent of dye in the serum after twenty-four hours. The urine urobilinogen was normal. A chest film on the eleventh postoperative day was normal.

The patient received two transfusions and numerous intravenous infusions but continued to become weaker. He finally became comatose; the temperature fell to 93.8°F., breathing became very slow, and he finally expired on the twenty-seventh postoperative day.

DIFFERENTIAL DIAGNOSIS

DR. CHESTER M. JONES: It is apparent from the first few paragraphs of the history that this patient had symptoms of ulcer, proved by x-ray and subsequently by operation. The only discrepancy is the x-ray examination, which implies that the ulcer was in the prepyloric region, but it actually turned out to be at the pylorus, where the incidence of malignant disease is much lower. He had diabetes on the first admission with a high blood sugar and glycosuria. Then there is the statement, which I am not willing to take at face value, that he had had cirrhosis. It is an interesting statement, and I wonder if it is true.

DR. BENJAMIN CASTLEMAN: Dr. Harwood, do you know whether this patient had had cirrhosis in the past?

DR. REED HARWOOD: His employer stated that the patient had vomited blood and that a diagnosis of cirrhosis had been made, but I think it would be fair for this discussion to say that at the first operation hepatic changes were not seen.

DR. JONES: I do not believe that there is any reason to say he had cirrhosis on the basis of the story or the findings. Everything is against it, and the hematemesis was probably due to ulcer rather than to esophageal varices. Against the diagnosis of cirrhosis at the time of the first admission are the facts that no liver or spleen was felt, that no x-rays were taken to demonstrate esophageal varices and that he had a dye retention at the end of thirty minutes of only 5 per cent or less. The diagnosis ought to be put in a pigeonhole as a very improbable background against which the rest of this picture is laid. Another variable is the hypertension on admission (systolic 210, diastolic 110), which subsequently disappeared. On the first admission one would be entitled to say that he had hypertension and hypertensive heart changes.

I know nothing about the operative findings. It would be interesting to know about the liver, the

gall bladder and the pancreas. In doing a subtotal resection the surgeon should have learned a good deal about these organs. I do not suppose, however, that it is possible to get this information at the moment.

DR. CASTLEMAN: It is not in the operative note.

DR. JONES: It should have been, but after a difficult operation, where the surgeon's main attention is directed toward a difficult diagnostic problem, the omission can be understood. The operative note should be as full as possible, and in my experience operations with detailed surgical notes are of immense value afterward.

DR. CASTLEMAN: The duodenum in the region of the ulcer was adherent to the pancreas, and no attempt was made to free it.

DR. JONES: The chances are that the patient did not have gross cirrhosis of the liver or cancer of the pancreas, since the surgeon would have noticed it. This patient had a striking loss of weight during the few months before the first admission, a drop from 155 to 123 pounds in a month. That could have been due to diabetes, and yet it does not seem that the diabetes was quite that severe. Possibly there was some associated disease which at that point had not come to light.

The next series of events came after the operation. He went home for three and a half months, and the diabetes, which may have caused the marked loss of weight and certainly caused increased thirst and polyuria, disappeared from the picture. He had no diabetic symptoms and was having insulin reactions on relatively small doses of insulin. He may have had only a mild diabetes. His appetite was poor after operation, and he had gaseous eructations after meals. After subtotal gastrectomies the majority of patients do extremely well, eat three good-sized meals without symptoms and gain weight rapidly. A fair number, on the other hand, do not have a good appetite and are unable to eat adequately without discomfort, even though their ulcer is cured. Then there is an intermediate group with a long convalescence and slow gain in weight. Three weeks before re-entry he became jaundiced and something new came into the picture that had not been found on careful physical examination three and a half months earlier—a mass that his physician thought was gall bladder. The liver was slightly enlarged and tender, and in addition, a lobular mass was found in the region where the gall bladder could and frequently does lie—the mid-clavicular line under the hepatic border.

The blood pressure, which had been 210 systolic, 110 diastolic, was 110 systolic, 70 diastolic. That is a rather striking single fact. I cannot explain it, unless it was associated with general loss of weight and of appetite and loss of body tone. It is a curious change.

On readmission we have further evidence that the diabetes was either nonexistent or extremely mild,

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BACILLARY DYSENTERY IN THE UNITED STATES

It is generally believed that dysentery is a disease primarily encountered in tropical and subtropical regions. As a matter of fact, epidemic and endemic bacillary dysentery occurs throughout the world, and although less of a public-health problem in the temperate than in the tropical zones, should be constantly kept in mind by all practicing physicians. The subject has recently been reviewed by Weil,¹ and several of its aspects deserve comment.

Bacillary dysentery is caused by a variety of organisms, including *Bacterium shigae*, *B. flexneri* (including a variant, the Newcastle strain), *B. sonnei* and *B. ambiguum* (Schmitz bacillus). Fortu-

nately, the organism causing the most serious type of dysentery, *B. shigae*, is practically unknown in the United States, the etiologic agents in order of frequency being *B. flexneri*, *B. sonnei* and the Newcastle bacillus. The last is more or less limited to the southern states.

Epidemics of dysentery are chiefly confined to institutions or hospitals for the care of patients with mental diseases or of children—in other words, where living quarters are crowded, where faulty habits of personal hygiene frequently exist and where the carrier rates are usually high. On the other hand, the disease occurs endemically throughout the United States. This is evidenced by the fact that in 1933–1937 vital statistics from twenty-one states recorded over 79,000 cases, with a mortality of 17.8 per cent, and since the actual death rate is believed to be about 2 per cent, this means that the total number of cases, reported and unreported, was in the neighborhood of 700,000. The fatal cases occur chiefly in infants and children; in fact, prior to 1910, diarrhea and enteritis were the most frequent cause of death in infants. Although these diseases have subsequently shown a remarkable decline in many sections of the United States, they are still only exceeded by prematurity as a cause of infant deaths in many southern states.

Infection is spread by direct contact with patients or healthy carriers and by food contaminated by such persons or by flies in areas where there are improper facilities for sewage disposal. The importance of the carrier problem is evidenced by the fact that dysentery bacilli have been cultured from 0.1 per cent of healthy persons in institutions in New York City and from 3.8 per cent in Georgia and New Mexico, from 28 per cent of healthy persons in families in which there had been a case of bacillary dysentery, and from 80 per cent of the inmates of a children's institution in which the disease had been present in epidemic form.

Control of the disease is dependent on adequate methods of sanitation and on the proper handling of patients and of carriers. The patient with bacillary dysentery harbors the causative organism in his intestinal tract for varying periods of time: nearly 3 per cent develop a chronic form of the disease, and 80 per cent of all patients yield positive

stool cultures for a month or more after the acute attack.

Of primary importance is full appreciation by the physician that the disease rarely causes the textbook picture of acute bacillary dysentery, general malaise with one or two days of slight fever, with or without loose stools, being the most frequent clinical syndrome. The patient should not be discharged until an appreciable number of negative cultures have been obtained—the British authorities recommend eight negative cultures in four weeks, or six in six weeks. Certain of the sulfonamide drugs, particularly those that are slowly absorbed from the intestinal tract,—such as sulfaguanidine,—have been claimed to be effective in ridding the bowel of the bacilli; in fact, a recent report states that in 208 cases, of which 190 were caused by *B. flexneri* and 18 by *B. sonnei*, that occurred among the armed forces in North Africa the stools were negative in 194 after one course of treatment with sulfaguanidine and those of the remainder became negative after a subsequent course of sulfadiazine.² Others have reported less successful results, particularly in cases due to *B. sonnei*, but this method deserves a thorough trial.

The detection of carriers presents a difficult problem. It is obvious that all carriers cannot be discovered, and even the examination of food handlers in institutions, hospitals, hotels, restaurants and the like has proved to be impractical. One of the most effective methods of lowering the incidence of the disease is the enforcement of proper personal-hygiene practices among food handlers.³

Although typhoid fever has been practically eradicated in temperate zones, it appears unlikely that the same results can be obtained with bacillary dysentery. On the other hand, there is no doubt that the incidence of the disease can be greatly lowered if proper precautions are observed.

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INJURIES TO THE EYES FROM AIR RIFLES

INJURY to the eye from the pellet of an air rifle is an all too frequent injury. Probably there is no time during the year when one cannot find on the wards of one of the Boston eye hospitals a patient whose eye has been injured in this manner. Usually the pellets, although they strike the eye with great force, do not perforate the globe. The violent contusion, however, may lead to the most serious complications. One often sees massive intraocular hemorrhage, dislocation of the lens, cataract, ruptures of the retina and choroid, and detachment of the retina. Seldom does an eye injured in this way escape permanent damage, and often permanent total blindness results.

This is truly preventable blindness. So long as air rifles are allowed to come into the hands of young people these injuries are bound to occur. The world would be no loser if this gun were outlawed. Since, however, there is no control over those who are permitted to use air rifles, every Massachusetts physician should comply with the law that requires the reporting of all such injuries and should conform to the other suggestions that appear in a letter published elsewhere in this issue of the *Journal*.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

DOWNING—Andrew F. Downing, M.D., of Cambridge, died June 2. He was in his sixty-seventh year.

Dr. Downing received his degree from Harvard Medical School in 1904. He was a member of the staffs of the Cambridge City Hospital, Boston Dispensary, St. Elizabeth's Hospital and the Massachusetts General Hospital. He was a member of the American Medical Association and a former president of the Cambridge Medical Improvement Society. His widow and two daughters survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN

CLINIC	DATE	CLINIC CONSULTANT
Salem	July 3	Paul W. Hugenberger
Haverhill	July 5	William T. Green
Brockton	July 13	George W. Van Gorder
Pittsfield	July 17	Frank A. Slowick
Worcester	July 21	John W. O'Meara
Fall River	July 24	Eugene A. McCarthy
Hyannis	July 25	Paul L. Norton

COMMUNICABLE DISEASES IN
MASSACHUSETTS FOR MAY, 1944

[DISEASES]	RÉSUMÉ		
	MAY 1944	MAY 1943	SEVEN-YEAR MEDIAN
Anterior poliomyelitis	1	1	1
Chancroid	3	*	*
Chicken pox	2560	1125	1207
Diphtheria	22	4	11
Dog bite	1421	1136	1259
Dysentery, bacillary	36	12	5
German measles	377	8077	259
Gonorrhea	440	360	358
Lymphogranuloma venereum	4	*	*
Measles	4209	6993	4118
Meningitis, meningococcal	54	74	8
Meningitis, Pfeiffer-bacillus	1	2	2
Meningitis, pneumococcal	3	11	†
Meningitis, staphylococcal	0	0	†
Meningitis, streptococcal	2	1	†
Meningitis, other forms	5	1	†
Meningitis, undetermined	9	23	†
Mumps	1438	645	943
Pneumonia, lobar	292	232	355
Salmonella infections	15	6	20
Scarlet fever	1513	1947	976
Syphilis	439	507	507
Tuberculosis, pulmonary	248	279	285
Tuberculosis, other forms	14	17	23
Typhoid fever	3	1	2
Undulant fever	7	3	3
Whooping cough	324	537	757

*Made reportable in December, 1943.
†Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

COMMENT

Chicken pox continues at a high level. The seasonal decline is also slow this year.

Diphtheria continues at a fairly high level as compared with last year. The figure for May is exactly twice the seven-year median.

Bacillary dysentery figures are high but most of the cases occurred in a large state hospital.

This is the third successive month in which meningococcal meningitis has been lower than in the corresponding month in 1943.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from: Newton, 1; total, 1.

Diphtheria was reported from: Belmont, 1; Boston, 4; Fairhaven, 1; Fall River, 1; Haverhill, 2; Lawrence, 3; Medford, 1; Melrose, 1; Somerville, 6; West Newbury, 1; Winthrop, 1; total, 22.

Dysentery, bacillary, was reported from: Boston, 1; Chicopee, 2; East Bridgewater, 1; Newton, 1; Worcester (State Hospital), 31; total, 36.

Encephalitis, infectious, was reported from: Billerica, 1; Worcester, 1; total, 2.

Malaria was reported from: Andover, 1; Boston, 2; Brookline, 2; Cambridge, 4; Camp Edwards, 7; Concord, 1; Cushing General Hospital, 9; Fort Banks, 10; Fort Devens, 19; Hanson, 1; Haverhill, 3; Holbrook, 2; Holyoke, 1; Medford, 5; Revere, 1; Salem, 1; Somerville, 3; U. S. Marine Hospital, Boston, 1; Wakefield, 3; Waltham, 1; Wareham, 1; Weymouth, 1; Woburn, 2; Worcester, 1; total, 82.

Meningitis, meningococcal, was reported from: Amherst, 1; Attleboro, 1; Boston, 19; Brockton, 1; Brookfield, 1; Cambridge, 2; Chelsea, 1; Easton, 1; Everett, 1; Fall River, 1; Fitchburg, 1; Hingham, 1; Lawrence, 2; Lexington, 2; Lowell, 1; Malden, 1; Millville, 1; Needham, 1; Newton, 1; North Attleboro, 1; Oxford, 1; Quincy, 2; Reading, 1; Salem, 1; Seekonk, 1; Somerville, 3; Springfield, 2; U. S. Marine Hospital, 1; Winthrop, 1; total, 54.

Meningitis, Pfeiffer-bacillus, was reported from: Monson, 1; total, 1.

Meningitis, pneumococcal, was reported from: Brockton, 1; Easthampton, 1; Ware, 1; total, 3.

Meningitis, streptococcal, was reported from: New Bedford, 2; total, 2.

Meningitis, other forms, was reported from: Boston, 4; Lynn, 1; total, 5.

Meningitis, undetermined, was reported from: Hingham, 2; Needham, 1; New Bedford, 1; Quincy, 1; Southbridge, 1; Springfield, 1; Weymouth, 1; Worcester, 1; total, 9.

Salmonella infections were reported from: Gardner, 1; Holden, 1; Malden, 2; Manchester, 3; Melrose, 1; Springfield, 1; Wellesley, 2; Worcester, 4; total, 15.

Septic sore throat was reported from: Boston, 10; Carver, 1; Everett, 1; Haverhill, 3; Hingham, 2; Lowell, 1; Malden, 1; Mansfield, 1; Quincy, 1; Winchester, 1; total, 22.

Trichinosis was reported from: Boston, 1; total, 1.

Typhoid fever was reported from: Attleboro, 1; Brockton, 1; Newton, 1; total, 3.

Undulant fever was reported from: Boston, 1; Bridgewater, 1; Danvers, 1; Egremont, 1; Fitchburg, 1; Great Barrington, 1; Shelburne, 1; total, 7.

CORRESPONDENCE

INJURIES TO THE EYES FROM AIR RIFLES

To the Editor: Since the start of the war there has been an alarming increase in the number of eyes seriously injured by BB guns. This is not surprising when one stops to note that children of all ages are war conscious, as evidenced by the preponderance of toys fashioned in military motives. The present law, a copy of which is appended, requires that all air-rifle injuries be reported to the Commissioner of Public Safety and to the police, regardless of the triviality of the wound.

The Massachusetts Division of the Blind is extremely anxious to get statistics on all BB-gun injuries. Its program of prevention of blindness can make no concession with the use of these dangerous toys by children, and it is exerting every effort to make illegal the sale of this weapon. Most of these injuries occur in children under sixteen years of age, and oftener than not, it is an innocent person who is the victim. The time to act is before an accident occurs. The non-magnetic character of the pellet makes for a poor prognosis in the eye, although it may do no serious damage elsewhere in the body. For the sake of many potential victims every physician in the Commonwealth is urged to:

Comply with the law requiring that all BB-gun injuries be reported to the Commissioner of Public Safety and to the local police department.

Drop a card to the Massachusetts Division of the Blind, 110 Tremont Street, Boston, stating that a case has been treated (regardless of what part of the body was struck).

Spread the word of the dangers of BB guns to all patients.

ARTHUR F. SULLIVAN, *Director*
Division of the Blind

110 Tremont Street
Boston

CHAPTER 112

Section 12A. Every physician attending or treating a case of bullet wound, gunshot wound, powder burn or any other injury arising from or caused by the discharge of a gun, pistol, BB gun, or other air rifle or other firearm, or, whenever any such case is treated in a hospital, sanitarium or other institution, the manager, superintendent or other person in charge thereof, shall report such case at once to the commissioner of public safety and to the police authorities of the town where such physician, hospital, sanitarium or institution is located. . . .

DEPRIVATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held May 17, the Board voted to revoke the license to practice medicine in this Commonwealth of Dr. Louis L. Hoff, Holyoke, Massachusetts, because of gross misconduct in the practice of his profession as shown by his conviction in court.

H. QUIMBY GALLUPE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

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PERFORATED PEPTIC ULCER*

A Follow-Up Study of One Hundred Cases

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BOSTON

DOES operative closure of an acutely perforated ulcer result in cure of the ulcer? Is acute perforation of a peptic ulcer an indication for gastric resection? What is the prognosis, and what regime should be recommended after a patient has recovered from the immediate episode of an acute perforation? In which cases is further surgery indicated?

The ensuing study was undertaken for the purpose of gathering information that would be helpful in answering such questions as the above and that, from a broader standpoint, would contribute to the establishment of sound criteria governing the follow-up management of perforated peptic ulcer. A number of papers dealing with perforated peptic ulcer have appeared in the literature during the past twenty years, but these publications have been concerned for the most part with the diagnosis and operative treatment of the acute perforation. In the present study, these latter aspects will be only briefly mentioned, emphasis being placed on the follow-up results and ultimate prognosis.

No attempt will be made to review the literature, since a fairly complete review was published by Sallick¹ in 1936.

MATERIAL

From the record files of the Boston City Hospital a complete roster was obtained of all the patients operated on for acutely perforated peptic ulcer at that institution from 1934 to 1941, inclusive. Those patients who died during the period of postoperative hospitalization were excluded, leaving about 300 patients who survived the immediate convalescence. These patients were requested by letter to return to the Outpatient Department for follow-up studies, and 104 of them complied. For simplicity of statistics the last four patients responding were not included in this study. They did not differ significantly from the preceding 100 patients, every one of whom

was interviewed and examined by me on one or more occasions, a gastrointestinal barium study being requested in each case. Patients who replied by letter or telephone and did not report in person were also excluded. Previous to this study, the majority of the patients had returned to the Outpatient Department on several occasions for follow-up examinations or treatment. Their previous outpatient records and the inpatient records in all cases were carefully studied. Every effort was directed toward making observations both impartial and accurate.

In the present series, 27 of the patients were in the fourth and 32 in the fifth decade at the time of perforation. The incidence falls steadily as one proceeds toward the younger and older age groups. The youngest patient was nineteen years of age and the oldest seventy-four. Ninety-seven patients were males and 3 per cent were females. This unexplained preponderance of perforation in the male sex has been noted in all previous studies.

The average length of the follow-up period was three years and four months, the longest period being twelve years and the shortest six months.

The ulcer was gastric in 54 cases, — prepyloric in 42 and located elsewhere in the stomach in 12, — duodenal in 40, and pyloric in 3; in the remaining 3 cases the exact site was not stated. In all cases the ulcers were in the anterior wall of the stomach or bowel. There were no cases of multiple perforations occurring simultaneously.

SURGERY OF THE ACUTE PERFORATION

The operative treatment of the acute perforation has been the source of considerable diversity of opinion. A review of the recent literature reveals, however, that a substantial majority of surgeons regard simple suture as the procedure of choice.¹⁻⁶ Gastroenterostomy is thought to be indicated in addition to simple suture only in cases in which the stomach is so encroached on as to make a probable complication.

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little justification for other procedures. It seems wisest to perform the simplest operation that will tide the patient over the emergency.

Simple suture alone was employed in 94 cases in this series. Local excision of the ulcer followed by suture of the resulting defect was performed in 2 cases. In 2 cases gastroenterostomy was performed along with simple closure of the ulcer. The ulcer was excised and pyloroplasty carried out in 1 case. Appendectomy was performed in addition to simple suture in 1 case, the original diagnosis having been acute appendicitis. It thus becomes obvious that this study is concerned almost entirely with the follow-up of patients treated by simple suture alone. The other procedures were too few to be of any statistical significance.

No effort was made to determine the operative mortality of the acute perforation among the 300-odd patients treated during the period from 1934 through 1941. However, Morrison,⁷ also working at the Boston City Hospital, in a statistical analysis of 200 cases of acutely perforated ulcer found the operative mortality to be 21 per cent. Although his study was carried out from 1930 through 1935, his figures apply in a general manner to the series of cases considered herein.

Following suture of the perforation, the average patient at the Boston City Hospital was maintained on parenteral fluids for one to four days and then started on frequent feedings of water, milk and cream, and Sippy powders. A week or ten days postoperatively a progressive convalescent Sippy diet was allowed. When discharged the patient was given printed instructions outlining an ulcer regime based chiefly on a full Sippy diet, the use of alkalis and tincture of belladonna and abstinence from alcohol and tobacco. The present paper is chiefly concerned with what happens to the patient from this stage on; that is, commencing with his discharge from the hospital.

FOLLOW-UP RESULTS

It is perhaps best to begin with a presentation of figures regarding the follow-up results in this study. These results were appraised as excellent in 28 cases, as good in 27, as fair in 22 and as poor in 23. Results were considered as excellent when there was no recurrence of symptoms, barium studies showed no ulcer activity and the patient was able to return to and remain at work. They were classed as good when mild symptoms such as occasional epigastric discomfort and belching of gas were experienced but did not interfere with work and were easily controlled by diet. They were described as fair when the patient experienced fairly frequent recurrences of symptoms and when there was occasional loss of time from work or the x-ray showed some evidence of ulcer activity such as marked spasm or an ulcer crater. The results

were considered poor when the symptoms were so constant and severe as to make attendance at work irregular or impossible or in which repeated hospitalizations were necessitated. In this category also fall the cases in which obstruction developed, second perforations occurred or further surgical procedures were performed for the relief of symptoms.

By pooling the excellent and good results on the one hand and the fair and poor results on the other, all the cases may be roughly grouped as satisfactory or unsatisfactory, there being 55 per cent in the former group and 45 per cent in the latter.

"The life history of ulcer can be said to end only with the life of the patient."⁸ Accordingly, it is obvious that the above classification of results does not represent a final analysis, since the average follow-up period was only three years and four months. It is significant, however, that of the patients who fell into the poor or fair categories, the vast majority had experienced recurrences of one sort or another within six months after perforation. In other words, what happens to a patient during the first six months to one year after perforation is a relatively accurate guide to his future course. Few patients who were symptom free for as long as a year had any serious recurrences at a later date.

DURATION OF SYMPTOMS PRIOR TO PERFORATION AS A GUIDE TO PROGNOSIS

It is a well-known fact that acute perforations often occur in persons who have never suffered from ulcer symptoms of any sort. There were 23 such cases in this group. Following perforation, 17 of these enjoyed a satisfactory result, and the remaining experienced difficulties such as to class them as having unsatisfactory results. There were 14 patients who had experienced symptoms for less than six months prior to perforation; 8 of these had satisfactory and 6 unsatisfactory results. In 57 cases symptoms had existed for from six months to many years prior to perforation; of this group, 25 patients experienced satisfactory and 32 unsatisfactory results. In summary, the longer the pre-perforation symptoms the poorer the postperforation results. Thus the presence or absence of an ulcer history prior to perforation has prognostic significance. Unsatisfactory late results were over twice as frequent among patients who had had symptoms for six months or longer as among those who gave no history of pre-perforation symptoms.

There were 31 patients who gave a history of severe symptoms prior to perforation. Of these, 23 had unsatisfactory and 8 satisfactory late results. Thus, a patient who has suffered markedly from ulcer symptoms prior to perforation, regardless of the duration of such symptoms, has about one chance in four of a successful late result.

INFLUENCE OF DIET, ALCOHOL AND TOBACCO ON RECURRENCES

The relation of diet, alcohol and tobacco to post-perforation recurrence of ulcer symptoms was investigated. Surprisingly, among a group of 25 patients who had made no effort to diet the recurrence rate was 40 per cent, whereas of 44 patients who had attempted to follow a diet it was 45 per cent. These figures serve chiefly to emphasize that there are factors that may be more potent than diet in determining the behavior of an ulcer. The patients who were able to remain well without dieting undoubtedly suffered from less virulent ulcer tendencies and found by experience that dieting was unnecessary. On the other hand, the patients who followed their diets for years did so for the most part because they had symptoms either in spite of dieting or whenever the diet was neglected. In short, their ulcers were of a more stubborn and potent nature. Thus, deductions that might be made from a statistical study of the relation of diet to ulcer are of limited significance. The same may be said of alcohol and tobacco. Many patients in this group partook moderately of alcohol and even excessively of cigarettes and yet remained symptom free.

Before the reader takes issue with the preceding paragraph, I hasten to state that there was a group of patients — namely, the 23 whose follow-up results were classified as poor — in whom adherence to diet and abstinence from alcohol and tobacco were of the utmost importance. Indiscretions along these lines in such patients precipitated symptoms almost as constantly as a barometer reflects changes in the weather.

As has been seen, the necessity for following a strict ulcer regime varies from patient to patient, and in any one patient is unpredictable at the outset. It is therefore essential to assume the worst and to insist on a strict regime for every patient indefinitely or until, over a period of years, his ulcer proclivities have been thoroughly assessed. If dietary liberties are allowed and are followed by a recurrence of symptoms, one should close the door forever on such liberties for that patient. It is far wiser to explain to every patient at the outset that he must adhere to an ulcer regime for the rest of his life and that the bars can be let down only at the peril of firing anew the embers of ulcer activity. It is a distressing and frequent experience to learn from a patient in the throes of recurrence that he was told by his physician that dietary restrictions were only an expedient to aid convalescence and could be dropped after that stage.

CORRELATION BETWEEN X-RAY EXAMINATIONS AND SYMPTOMS

Barium studies were first ordered in all cases in which symptoms were severe. Then, since some

patients apparently have ulcers that, although active, are relatively asymptomatic, it was decided that x-ray examination should be made in all cases. Seventy-eight of the 100 patients reported for this examination. Eight additional patients had had such an examination fairly recently, so that barium studies were available in 86 of the 100 cases.

X-ray films were considered positive for ulcer, either active or chronic, under the following circumstances: when an ulcer crater was visualized; when there was pyloric obstruction with a gastric residue; and when persistent marked tenderness and spasm of the duodenal cap were noted in repeated studies.

Measured by the above criteria, x-ray examination showed ulcer activity in 50 (58 per cent) of the 86 patients who were subjected to such studies. Of these 50, symptoms varying from moderate to severe were present in 40 cases (80 per cent), and no symptoms whatsoever had been suffered in 10 (20 per cent). Barium studies were negative for ulcer activity in 36 cases (42 per cent). Twenty (55 per cent) of these patients were asymptomatic and 16 (45 per cent) had suffered from symptoms, which were mild in 12 cases and severe in 4.

It may be seen from the above that the x-ray findings were in complete agreement with the symptomatology in 69 per cent of the cases examined; there was only a slight divergence between these two factors in another 14 per cent, and there was no correlation whatsoever between the symptoms and the x-ray findings in 16 per cent. These latter discrepancies may be explained partly on the basis of inaccuracies in x-ray diagnosis on the one hand and the unquestionable existence of silent ulcers on the other. Deformities resulting from the surgical treatment of the acute perforation are difficult to evaluate and to differentiate from ulcer. Also, the significance of spasm and tenderness is always open to question. In short, it is important to realize that x-ray and fluoroscopy have limitations and that decisions should never be made through these mediums alone.

SECOND PERFORATIONS

Three patients experienced a second acute perforation. One of these patients was sixty-seven years of age. He had suffered from symptoms prior to his first perforation but said that his second came "out of a clear sky" ten months later. He has not followed a strict diet since this last perforation, drinks beer freely, has an active duodenal ulcer as shown by x-ray examination and has recurrent symptoms. Surgery was advised but refused. This patient will undoubtedly experience further trouble.

Another of these patients was seventy-four years of age. He had had symptoms for twenty years prior to his first perforation. The second perforation came eight years later, the interval being marked by transient moderate symptoms. He has had

severe recurrent symptoms, and recent x-ray examination showed an active prepyloric ulcer. This patient improved after strict dieting. Surgery was withheld because of his age and because he presented a poor surgical risk.

The third patient was forty-six years of age. He had experienced symptoms for only fifteen hours prior to his first perforation, which was duodenal. Four years later he experienced a second perforation, also duodenal. The interval was marked by symptoms and failure to follow a diet. A recent barium study showed a penetrating duodenal ulcer. This patient is awaiting gastric resection, which has been advised.

These experiences, although brief, are typical of others reported in the literature.

For several reasons it is concluded that a second perforation should be considered an indication for elective subtotal gastric resection. First, an ulcer that perforates twice is of a virulent, persistent nature and is likely to lead to further grave complications. Second, these patients have not adhered strictly to an ulcer regime in most cases, even though vividly aware of the consequences of laxity in this regard. If a patient does not conform to restrictions after he has experienced one perforation, there is little cause to assume that he will ever do so. Of course, if following an acute perforation a patient is told that an ulcer regime is unnecessary or is told nothing and fails to adhere to a regime through ignorance of it, he cannot be held at fault if a second perforation occurs. He is still entitled to a trial of medical treatment, and not unless he has recurrence under such treatment should he be subjected to surgery.

CARCINOMA IN A GASTRIC ULCER

Carcinoma apparently developed in a gastric ulcer in one of the cases of this series. The patient was fifty years of age. At the time of perforation the lesion was prepyloric and on the lesser curvature. Carcinoma was suspected because of widespread induration, but biopsy showed only chronic inflammation. X-ray films were negative one year after perforation and the patient was free of symptoms for two years, but then began to lose weight and to experience severe epigastric pain and vomiting. The x-ray diagnosis was prepyloric carcinoma. A subtotal gastric resection was performed and an easily resectable colloid carcinoma of moderate size was found in the exact site of the previous ulcer. This patient has remained free of symptoms for four months.

The possibility of the development of carcinoma is certainly to be kept in mind and is an added reason for leaning toward subtotal resection for chronic gastric ulcers, especially in cases in which ulcers have perforated. Walters⁹ believes strongly that surgery is indicated for chronic gastric ulcers in general.

SECONDARY SURGICAL PROCEDURES

Secondary surgical procedures were performed in 11 patients of this series. The indications were as follows: intractability, 5 cases; pyloric stenosis, 4 cases; carcinoma, 1 case; and possible carcinoma, 1 case. Subtotal gastric resection was performed in 7 of these cases. There was no operative mortality, and all these patients have remained symptom free for one to six months. Posterior gastroenterostomy was performed in 3 cases. These patients have remained well for nineteen to seventy-two months.

Partial gastric resection, excluding the ulcer (duodenal) by leaving the pylorus, was performed in 1 case. The pyloric and adjacent antral mucosas were not excised. The patient died following a perforation through the suture line of the gastroenterostomy, the perforation occurring on the nineteenth postoperative day. This patient had had a high gastric acidity, had had two massive hemorrhages in addition to his perforation and had suffered from severe ulcer pains. A subtotal gastric resection including the ulcer was indicated and would probably have been curative.

There are too few cases in this group and the follow-up periods are too brief to make further discussion of the operative results worth while.

There were 12 additional patients whose ulcer symptomatology and x-ray findings were such as to call for subtotal gastric resection. Most of them refused operation. In 3 cases they were such poor risks that surgery had to be withheld.

Combining the 11 patients who had secondary surgical procedures with the 12 who should have had them, one obtains a group of 23 cases in which further surgery was indicated. In other words, in almost one fourth of the cases the follow-up results were sufficiently discouraging to make elective surgery feasible.

COMMENT

Gastric analyses were not routinely carried out in all these cases because of limited time and facilities. It is regretted that the total number of such analyses performed was not sufficient to permit a significant correlation between gastric acidity and the other factors considered in the follow-up study.

The importance of the psychic factor in the causation and aggravation of peptic ulcer is clearly recognized. It was suggestive in many of these cases that personality was a dominant cause of the ulcer difficulties. Since this factor, however, is too complex to lend itself to accurate evaluation it did not seem practical to include it in the study. The psychic factor is also the most inaccessible from a therapeutic standpoint, and it is probable that since this factor exercises a strong influence on gastric motility and secretion,¹⁰ it is the one chiefly at fault in the ulcers that are the most stubborn and virulent in the face of medical treatment.

There seems to be a tendency among physicians and surgeons to cling to dietary efforts through an unwarranted siege of ulcer recurrences. If a patient, following a perforation, has had his condition explained to him and a regime, including diet, outlined and has still had two or more recurrences of serious symptoms in spite of his efforts to follow instructions, the physician should face the facts. He should remember that an ulcer regime has decided limitations, even when followed to the letter. Human nature greatly widens these limitations. If a patient has failed to adhere to a regime several times, there is little justification for supposing that he will do so in the future. The average patient adheres to instructions only so long as he has symptoms. Rather than theorize as to what would happen should the patient adhere strictly to instructions, one should consider what has already happened and make a decision based on facts rather than on theory. Were this done oftener, many more of these patients would come to surgery earlier in their ulcer careers and be spared no end of physical, social and financial suffering. Chronic alcoholic patients and those who are totally uncooperative from a medical standpoint should not be subjected to elective surgery, for surgery is no cure-all. Unless a patient is reasonably careful he may find himself saddled with a marginal ulcer at the gastroenterostomy even though a technically good operation has been performed.^{8, 11}

The 25 per cent of patients suffering from severe recurrences should be subjected to surgery. The indications for surgery in peptic ulcer have been outlined many times. They are as follows: two or more massive hemorrhages, pyloric stenosis with obstruction, intractability and possible malignancy. To these generally accepted indications it seems wise to add the following: patients experiencing acute perforation of an ulcer for the second time, those experiencing acute perforation, preceded or followed by one or more massive hemorrhages, those experiencing severe recurrent ulcer symptoms following perforation and those experiencing perforation as a climax to a protracted ulcer history. It should be stressed that acute perforation is not in itself regarded as an indication for gastric surgery, since over half the patients do satisfactorily on a conservative regime following such perforations. This is an effective answer to those who advocate gastric resection as the procedure of choice at the time of the perforation. Neither should any patient be subjected to elective gastric surgery unless he has given medical treatment a thorough trial and failed to obtain relief.

When elective surgery becomes necessary the same procedure is indicated in ulcers that have perforated as in those that have bled or become obstructive; namely, subtotal gastric resection. This is not only the procedure of choice but is the only one that consistently gives excellent results. By subtotal resection is meant the removal of two

thirds to three fourths of the stomach together with the pylorus, closing the duodenal stump blindly and re-establishing the continuity of the gastrointestinal tract through some form of gastrojejunostomy. If a pyloric or duodenal ulcer is technically hazardous to remove, subtotal resection may be performed, leaving the pylorus and ulcer in situ; this is the so-called "exclusion operation." If it is employed,¹² all antral and pyloric mucosa must be thoroughly excised before closing the pyloric stump. There is one set of circumstances in which gastroenterostomy alone is an acceptable procedure; namely, in an elderly patient having a high degree of pyloric stenosis and an extremely low gastric acidity.

The operative mortality from subtotal gastric resection in the better surgical clinics varies from 2 to 10 per cent. The mortality following this operation is no greater than that following the lesser procedures such as gastroenterostomy.¹² According to Walters,⁹ Wangenstein¹³ and any number of others with wide experience in this field, results following adequate surgery are excellent in 90 per cent or more of the cases. These facts are not new but that they are not fully appreciated by physicians is evidenced by the number of persons suffering from chronic ulcer that are found in the average American community.

In conclusion, two admonitions should be made concerning radical gastric surgery.

First, there are too many surgeons who speak in terms of subtotal gastric resection but who perform a partial gastric resection; who, in other words, resect less than half the stomach for the cure of ulcer. The technic of gastric resection has been standardized and repeatedly published by many of the most competent gastrointestinal surgeons. If one hopes to approach the excellent results appearing in the literature, he must begin by conforming to the principles and technic that yielded these results. Meticulous attention to every detail is essential. Neglect of any one may be fatal.

In the second place, and in line with what has just been said, gastric surgery is no field for the amateur. The consequences of a technically poor operation may be infinitely more distressing than those of a chronic ulcer. The indications for gastric surgery should be considered in relation to the ability of the surgeon.

SUMMARY

A follow-up study of 100 cases of perforated peptic ulcer is reported.

The average length of the follow-up period was three years and four months.

The incidence of perforation was maximum in the fifth decade. There were 97 males and 3 females.

The ulcers were gastric in 54 per cent of the cases, duodenal in 40 per cent, and in 3 per cent

Simple suture was performed for the acute perforation in 94 per cent of the cases.

The follow-up results were considered excellent in 28 per cent, good in 27 per cent, fair in 22 per cent and poor in 23 per cent of the cases.

In cases in which the symptoms prior to perforation are severe or protracted, the prognosis is poor.

Diet, alcohol and tobacco in the majority of cases are not the most important factors governing recurrences; psychic disturbances and lack of co-operation on the part of the patient, however, play significant roles.

Gastrointestinal x-ray studies were in accord with the symptomatology in 67 per cent of 86 cases.

Second perforations occurred in 3 cases. Carcinoma developed in an ulcer in 1 case.

Secondary surgical procedures were performed in 11 per cent of the cases.

Suggestions are made regarding several additional indications for elective surgery in cases of peptic ulcer.

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POLIOMYELITIS ON THE ISTHMUS OF PANAMA*

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ANCON, CANAL ZONE

ENDemic poliomyelitis is now recognized as being world-wide in its distribution; it is also thought to be one of the oldest human diseases.¹⁻⁶ In spite of this, only a few recent studies^{7,8} of the epidemiology of endemic cases have been made. The more dramatic epidemic outbreaks, which have appeared principally in the temperate zones during the last fifty years, have been studied with great profit. The knowledge of the epidemiology of poliomyelitis is still extremely incomplete, and studies in endemic areas may contribute to it.

The widespread geographical distribution of poliomyelitis indicates that all races are susceptible to the disease. The relative susceptibility of the various races is, however, difficult to determine. Harmon⁵ summarized the results of studies in the United States and concluded that Negroes seem to be less susceptible to infection than are Whites, but that once infected their mortality rate is apparently higher. Lee⁹ in Hawaii found high incidence rates among Caucasians and native Hawaiians but low rates among Filipinos, Chinese and Japanese. Among the Caucasians there was a fairly general distribution through all age groups, whereas among the Orientals most of the cases were in children under five years of age. In the 1934 epidemic in the Philippine Islands, Hillman¹⁰ stated, most of the cases occurred in white adults.

No previous studies of poliomyelitis on the Isthmus of Panama have been made. The 72 cases

included in this report have been treated at Gorgas Hospital (formerly Ancon Hospital) in the thirty-eight years from 1904 to 1942. During this time there have been over 530,000 hospital admissions, with an average incidence of 1 case of poliomyelitis in 7000 admissions. Most of the cases recognized in the Canal Zone and the Republic of Panama are included in this series, but because of the extreme variability of the base population it has been impossible to derive true incidence rates. Eight hospital cases were not included in the study group because they did not meet rigid diagnostic standards or because the infection had not been contracted on the Isthmus.

SEASONAL DISTRIBUTION

The annual distribution of all cases is recorded in Table 1. For comparison, there is included the total number of cases reported to the Health Department of the Panama Canal.¹¹ The minor discrepancies can be explained either by the fact that some hospital cases were drawn from a slightly wider geographical area than the others or by the fact that some of the cases included in the Health Department records were treated in other hospitals. Local endemicity is clearly indicated by the sprinkling of cases, with an average of slightly greater than 2 cases per year. A minor epidemic pattern is apparent when the cases are carefully analyzed for spatial and temporal proximity. In seven instances there was evidence of contact between

*From the Board of Health Laboratory, Gorgas Hospital.

groups of 2 to 5 cases. These contact groups are listed in Table 2.

The most significant feature of the seasonal distribution, as indicated in Table 3, is the monthly

TABLE 1 Annual Distribution of Poliomyelitis

YEAR	HOSPITAL CASES	CASES REPORTED TO HEALTH DEPARTMENT
1907	1	0
1911	1	0
1912	3	1
1915	0	1
1916	2	2
1917	0	1
1918	1	1
1919	0	1
1920	4	2
1921	2	3
1922	3	2
1923	0	1
1924	5	7
1925	10	8
1926	4	4
1927	3	5
1928	6	5
1929	3	3
1930	1	1
1931	4	2
1932	2	5
1933	4	4
1934	3	6
1935	1	1
1936	1	1
1937	1	1
1939	3	1
1940	3	3
1941	2	5
1942	0	—
Totals	72	77

incidence curve. A distinct unimodal peak occurred during November, December and January. All but one of the minor epidemics took place near the crest of this curve.

RACIAL

Twenty-nine cases occurred in Whites, 26 in West Indian Negroes, 12 in Panamanians, 3 in Colombians, 1 in an Ecuadorian and 1 in a Chinese.* That

TABLE 2 Contact Groups

TIME	PLACE	CASES	AGE
December 1916	Balboa	2	5
November 11 to December 11 1920	Cristobal and Silver City	1	6 and 11
April 4 to May 4 1924	Colon	1	2-4
September 25 to October 9 1925	Pedro Miguel	5	2-7
December 20 1926 to January 2 1927	Panama City	2	3 and 5
November 23, 1931 to January 23, 1932	Silver City and Colon	3 Negroes and 1 Chinese from neighboring localities	1-2
September 27 to October 11 1933	Balboa	2 white girls (close friends)	6 and 9

the incidence in Whites is truly greater than that in Negroes is demonstrated by breaking down the figures for the Canal Zone. Only a few mestizos of Panamanian origin reside in the Canal Zone, and these are customarily included in the Negro or so-called "silver" group in Canal Zone statistics. The Canal Zone School Division has reliable statistics

*The term "race" as used here is a purely utilitarian break down of the local color groups. Whites are United States citizens and other Caucasians. West Indian Negroes include the original relatively pure Negro group imported for the construction of the Panama Canal and their children. Panamanians include the mixed Spanish Indian and Negro natives of the Republic of Panama.

on the number of white and negro children living in the Canal Zone from 1928 to the present. The ratio of the total groups is approximately 3 Whites to 5 Negroes. In the 40 cases of poliomyelitis occurring primarily in the Canal Zone the ratio was 5.3. This means that poliomyelitis was two and three-fourths times as common in the Whites as in the Negroes.

AGE

Seventy-two per cent of the patients in this series were five years of age or less, with a median age of three. The contrast in the age distribution of the

TABLE 3 Seasonal Distribution

MONTH	No. of CASES
January	10
February	5
March	5
April	3
May	3
June	2
July	3
August	5
September	6
October	8
November	12
December	10

racial groups is striking. Fifty-two per cent of the Whites were five years of age or under, as compared with 85 per cent of the Negroes and 83 per cent of the Panamanians. The white population of the Isthmus of Panama has had an unusually large young-adult group. This has little significance, however, because 83 per cent of the Whites were ten years of age or under and only 2 were over twenty.

SEX

The total group showed the usual distribution of 43 males to 29 females. In the Whites and Pan-

amanians there were twice as many males as females. Among the West Indian Negroes, however, the incidence was equal in the two sexes.

Geographical

In general, the geographical distribution followed that of the population. In the Republic of Panama, Panama City and Colon each had 13 cases, in the Canal Zone, Balboa had 9 and Pedro Miguel 5 cases came from the interior of

CLINICAL PICTURE

As is true in most endemic areas, the diagnosis of poliomyelitis was rarely made in the absence of paralysis. The average duration of symptoms prior to hospitalization was six and a half days—five days among the Whites, six days among the Panamanians, and eight and a half days among the West Indian Negroes.

The clinical picture was typical, the following symptoms and signs being recorded: fever, 58 cases; nausea, vomiting and anorexia, 32 cases; constipation, 7 cases; diarrhea, 1 case; headache, 15 cases; drowsiness, irritability or coma, 15 cases; mild convulsions or opisthotonos, 8 cases; early positive Brudzinski's or Kernig's signs, 6 cases; and urinary difficulty, 4 cases. Spinal-fluid determinations showed the usual lymphocytosis and increase in globulin.

Only 4 patients were free from paralysis, the diagnosis being made from prodromal symptoms and muscle tenderness in a close contact of a paralytic case. The distribution of the paralyzed muscle groups is shown in Table 4. The average period

TABLE 4. *Distribution of Paralyzes.*

LOCATION	PRIMARY PARALYSES	RESIDUAL PARALYSES
Legs:		
Right	41	40
Left	43	29
Arms:		
Right	14	8
Left	11	9
Back	13	7
Abdomen	2	1
Respiration	1	
Neck	5	1
Oculomotor	4	1
Facial	2	0
Deglutition	3	0
None	4	15

of hospitalization was thirty-eight days. The residual paralyzes at the end of this time are also indicated in Table 4.

There were 5 deaths, a mortality of 6.9 per cent. Four of the fatal cases were in Whites and 1 was in a Panamanian. No deaths occurred in the West Indian Negro group. The autopsy reports record the usual neuronal damage and inflammatory reaction.

DISCUSSION

The seasonal distribution of these cases is of interest because of the distinctive climatic conditions prevailing in Panama. The latitude of Panama is about 8° north, well within the tropics. The temperature is monotonously uniform, rarely varying from the narrow range of 68 to 95°F. The incidence of poliomyelitis in most localities shows a direct correlation with warm weather, and it has been stated that in warm climates there is a tendency toward an even distribution throughout the year.¹² Lee⁹ found a seasonal curve in Hawaii, with a prolonged crest extending from February to June. In Panama the variable of temperature is so nearly

controlled that one must search for correlations with other factors.

Panama has only two seasons, the wet and the dry—the latter appearing in January, February and March. With the crest of the poliomyelitis curve occurring in November, December and January one cannot say that either season is particularly favorable for transmission. Instead, it may be that the transition from wet to dry weather is important just as it is thought that the transition from warm to cold weather is important in temperate zones. Most recent studies indicate that rainfall is a negligible epidemiologic factor in other localities.^{1, 4, 5} The seasonal distribution of gastrointestinal diseases in Panama is not well defined. Conner and Bates¹³ reported that from 1919 to 1923 most of the cases of bacillary dysentery at Gorgas Hospital occurred in October, November and December. Macumber¹⁴ stated that in his series of 263 cases of bacillary dysentery in the eleven-year period from 1928 to 1939 there was no significant seasonal variation. A review of his data, however, reveals that the peak month was February with 53 cases and that from October to March there were 170 cases, as contrasted with 93 cases in the six months after the onset of the rainy season. These data show a suggestive correlation between the seasonal distribution of cases of poliomyelitis and bacillary dysentery admitted to Gorgas Hospital.

The racial distribution of poliomyelitis raises several interesting questions. The greater incidence in Whites is difficult to explain. Aycock's¹⁵ autarceologic distinctions suggest intriguing possibilities, and further studies may make it possible to apply them to racial groups. It seems significant that in both Hawaii and Panama the native populations showed involvement in distinctly younger age groups than did the Whites. Reports from the United States,¹⁶ Scandinavia¹⁷ and Australia^{18, 19} all record a distinct shift in the age incidence of poliomyelitis during the last few decades. In earlier epidemics poliomyelitis was characteristically an infantile disease, but most of the recent studies in the predominantly Caucasian large epidemic centers show definitely that older age groups are being afflicted. In Portugal, d'Oliveira²⁰ reported an infantile distribution. A partial explanation that may be proposed hinges on the possibility that abortive attacks or subclinical infections have caused widespread early immunization in the temperate zones in years gone by, and that this condition still prevails among the native populations of the tropics. If one accepts the enteric route of infection, it is not difficult to postulate delayed immunization among Caucasians coincident with an improvement in sanitation. The presence of this nonimmune group would be conducive to the spread of epidemics in the temperate zones. The studies with protection neutralization

tests on monkeys, although these are admittedly crude, lend credence to this hypothesis, since protective bodies have been demonstrated with great uniformity in the blood of the native populations of several tropical and subtropical countries.²¹⁻²³ It is hoped that neutralization tests of greater specificity will be developed as a result of Armstrong's²⁶ transmission of the virus to the cotton rat, and that this will permit a more accurate delineation of the true geographical and racial distribution of poliomyelitis.

SUMMARY

Seventy-two cases of endemic poliomyelitis on the Isthmus of Panama have been reviewed.

The crest of the seasonal curve occurs during November, December and January—the end of the rainy season.

Poliomyelitis was two and three-fourths times as common in Whites as in Negroes.

Among the Whites 52 per cent of the patients were five years of age or under, as contrasted with 85 per cent of the West Indian Negroes and 83 per cent of the Panamanians.

There were twice as many males as females among the Whites and Panamanians, but the incidence in the two sexes was equal in the West Indian Negroes.

There were 5 deaths, a mortality of 6.9 per cent. Most of the cases occurred in the large population centers.

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X-RAY THERAPY OF THE HEART IN A PATIENT WITH LEUKEMIA, HEART BLOCK AND HYPERTENSION*

Report of a Case

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BOSTON

THIS is the case report of a woman who was followed for years because of vascular hypertension and who later developed myelogenous leukemia and then heart block. Since leukemia is known to infiltrate the heart muscle, it was thought that possibly a leukemic infiltration or a leukemic nodule in the heart was interfering with the conduction mechanism of the heart beat and was the

cause of the heart block. If this were true, it seemed that x-ray therapy applied directly to the heart might cause the block to disappear. There are no reports in the literature of heart block treated in such a manner. Because of the result obtained with x-ray therapy in this case, it appeared of interest to present its details.

CASE REPORT

A 64-year-old widow was known to have had a blood pressure of about 200/100 for 20 years. The blood pressure had been frequently observed during this period, and on rare occasions it rose to 250/110 and dropped to 160/90.

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The records of this case begin in 1925, when the patient was at the old Beth Israel Hospital, where diagnoses of hypertension and chronic myocarditis were made. The examination was negative except for obesity, a precordial systolic murmur and hypertension. A blood Wassermann test was negative. The nonprotein nitrogen was 40 mg. per 100 cc. and the fasting blood sugar 110 mg. The heart was enlarged as shown by x-ray examination, the transverse diameter being 15 cm. and that of the chest 26.5 cm.

In 1933, the patient was admitted to the Beth Israel Hospital for possible cholecystitis, possible coronary disease and hypertensive heart disease. There was a systolic murmur over the precordium. The blood pressure varied from 235/120 to 160/90 and the pulse from 70 to 80. The white-cell count ranged from 19,600 to 9200, with no abnormal cells. The hemoglobin was 80 per cent, and the red-cell count 5,750,000. The body weight was 200 pounds. Electrocardiograms showed left-axis deviation. The urine gave a ++ test for bile on several occasions. The fasting blood sugar was 78 mg. per 100 cc., and the nonprotein nitrogen 32 mg.

From 1933 to 1940, the patient suffered from indefinite abdominal pains, nervousness and many headaches. The heart was regular, with a moderate rough precordial systolic murmur. The blood pressure was usually 200/100. She took many sedatives, and a great deal of Pyramidon for the headaches. Because one of her sons, a physician, feared leukopenia and agranulocytosis resulting from the continued use of Pyramidon, a number of white-cell and differential counts were made; these were found to be normal. In April, 1940, however, the patient had gallstone colic with jaundice, and the white-cell count during this episode ranged from 13,000 to 15,000, returning to normal after the attack disappeared. The weight was 165 pounds, and the pulse 70 to 80.

On March 9, 1941, the patient was admitted to the Peter Bent Brigham Hospital because of marked cyanosis, dyspnea, precordial distress, a temperature of 102°F. and profuse sweating. On admission the pulse was 72 and the blood pressure 204/90. The weight was 141 pounds, and there was evidence of considerable weight loss. The heart was enlarged, and there was a coarse systolic murmur over the precordium. The breath sounds were harsh, and there were a few rales at the lung bases. The liver and spleen were not palpable. The white-cell count was 127,000, with 86 per cent neutrophils, 9 per cent lymphocytes and 5 per cent myelocytes. The hemoglobin was 54 per cent (Sahli) and the red-cell count 2,900,000. The nonprotein nitrogen was 41 mg. per 100 cc. Electrocardiograms (four leads) were normal except for evidence of left-axis deviation.

On the 2nd hospital day the temperature fell to normal, where it remained thereafter. Blood Wassermann and Hinton tests were negative. X-ray examination of the chest showed marked cardiac enlargement and moderate congestion of the lungs, chiefly around the hili. Films of the right shoulder and humerus showed the bones and joints to be rather thin, and the marrow cavity considerably wider and clearer than usual, which it was believed might indicate hyperplastic bone marrow.

Basal metabolism tests on eight occasions were elevated, the first rate being +55 per cent and the subsequent ones varying from +39 to +25 per cent. There was little change in the metabolism after the giving of Lugol's solution. The diagnosis was myelogenous leukemia, hypertension and cardiac decompensation.

The patient was digitalized on entry and then given 0.1 daily. Lugol's solution, 10 drops three times prescribed. X-ray therapy in the form of a n to the trunk anteriorly and posteriorly in of 25 r each — not a large dose. Following cell count dropped to 8650 by March 26;

he entire trunk, alternating front and back, is 5 to 50 r a day to patients with leukemia, and are efficient and better tolerated than concen-spleen or long bones with larger doses. The a filter of 0.5 mm. of copper and 1.0 mm. of skin distance of 100 cm. At this distance the re trunk. Only the face and head are covered te with a standard Victor chamber with This method has proved extremely chronic leukemias. It does not cause y results in prolonged regressions. In daily are used, but the results are not so

the red-cell count was 3,000,500 and the hemoglobin 88 per cent (Sahli). The patient was discharged improved on April 11 with a white-cell count of 8650 and a weight of 135 pounds. She was instructed to take 0.05 gm. of digitalis daily and 10 drops of Lugol's solution daily, as well as iron

After this treatment the patient continued to improve, gained weight and was fairly active. The medication was taken as prescribed. The pulse remained at 72, and the blood pressure at 210/100. On September 6, the basal metabolic rate was +14 per cent, the pulse 72, and the weight 155 pounds. The white-cell count was 10,600, the hemoglobin 70 per cent, and the red-cell count 4,310,600. On October 21, however, when the white-cell count was 14,500, the patient began to feel tired. The white-cell count subsequently increased slowly, reaching 31,900 by March 1, 1942. X-ray therapy was again given on March 4 and 5 in the form of a spray to the trunk anteriorly and posteriorly in two treatments of 25 r each, and in 9 days the white-cell count dropped again to 9000 and the patient felt much better.

In April the patient again commenced to feel tired, weak and conscious of her heart beat and began to have a slow pulse (36 to 48), which persisted until August, the blood pressure remaining at about 210/100. The digitalis was omitted shortly after the pulse slowed, but in spite of this, the low rate persisted even though there was no coronary pain or decompensation. On July 8, when the white-cell count was 19,600, electrocardiograms showed a 2:1 heart block and left-axis deviation.

At that time it was thought that in the presence of leukemia, a leukemic nodule or infiltration involving the bundle of His might be the cause of the heart block and that x-ray therapy to the heart might cause the nodule to decrease in size and the block to disappear. It was believed that if x-ray therapy of the heart had an effect, this would begin after four or five days of treatment, because following such a period of x-ray therapy in leukemia the white-cell count usually falls appreciably. Consequently, it was decided to treat the patient in this way in the hospital. She was admitted to the Peter Bent Brigham Hospital on August 6 for x-ray therapy of the heart and was discharged on September 2. The pulse was 38 and the blood pressure 208/80. The weight was 165 pounds. The heart action was slow and regular. A third heart sound was audible, which may have been due to auricular contraction and had been present since the heart block appeared. In addition, a moderate rough systolic murmur was present over the precordium. Electrocardiograms again showed a 2:1 heart block and left-axis deviation. The white-cell count before x-ray therapy ranged from 22,000 to 24,500. The hemoglobin was 89 per cent (Sahli) and the red-cell count 4,490,000. The basal metabolic rate before x-ray therapy was +15 and +20 per cent. The blood urea nitrogen was 28 mg. per 100 cc.

X-ray therapy was directed to the heart on August 11, 12, 13, 17 and 25. The treatments given directly to the cardiac area were at the standard target-skin distance of 50 cm., using 200 kv., and a filter of 0.5 mm. of copper and 1.0 mm. of aluminum. With these factors the ionization rate measured in air was 65 r per minute. Daily doses of 200 r to the precordium were given, using a cone 15 cm. in diameter. The total skin dose in five treatments during 15 days was 1000 r.

On August 14, the pulse, which had been between 36 and 42, rose to 72 to 80 during auscultation and the third heart sound disappeared. The heart again went into block, however, and apparently was in a transitional state of being in and out of block. Electrocardiograms were taken of these phases during auscultation (Fig. 1). The pulse remained at about 80 much of the time and periodically dropped to 42. The murmur of the heart was of less intensity when it was unblocked than when it was blocked.

During the period of hospitalization a 7-foot film of the heart gave evidence of fairly marked cardiac enlargement. Fluoroscopy showed a slow beat of large amplitude with systolic expansion of the right pulmonary artery. The right auricular beat appeared in approximately 2:1 rhythm when the patient was in heart block. In the mitral annulus fibrosus there was an area of calcification that moved with the auricular beat and not with the ventricular pulsation. The heart had a transverse diameter of 17.8 cm. and the chest an internal diameter of 29.5 cm. Re-examination of the heart by x-ray when it was not in block showed its size and shape to be almost identical with those noted 11 days previously when the heart was in block.

The patient was discharged on September 2. The pulse remained at a level of 72 for 6 days and then dropped to 42, where it remained (Fig. 2). It stayed at this level until after further x-ray treatment of the heart, beginning on Novem-

ber 23, when the heart again went into 2:1 block, with a pulse of 48. When the white-cell count increased to 27,000 on February 4, it was decided to give x-ray spray therapy to the trunk anteriorly and posteriorly to discover whether reducing the

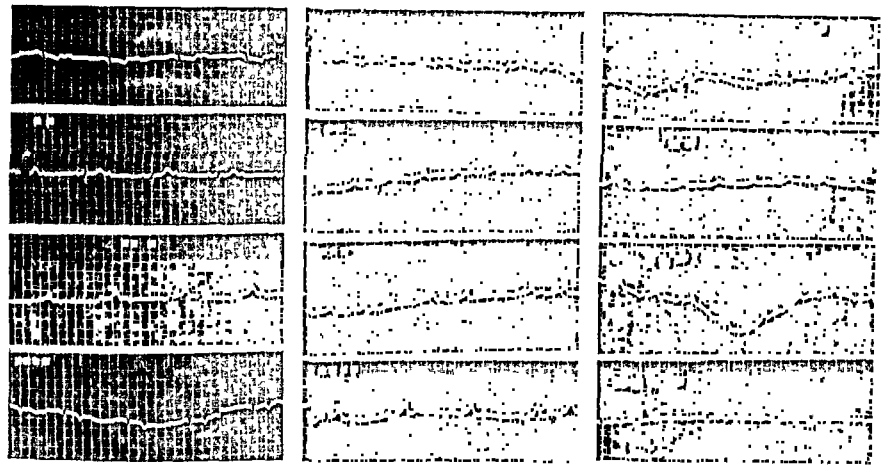


FIGURE 1. Electrocardiographic Changes after X-ray Therapy.

The tracings on the left, taken on August 11, before treatment, show 2:1 heart block with an auricular rate of 84 and a ventricular rate of 42. The middle tracings, taken on August 14, after treatment, show that the heart was in and out of block, normal sinus rhythm alternating with 2:1 block, T_4 is upright. The tracings on the right, taken on August 19, show normal rhythm with a rate of 77; T_4 is inverted. In all sets, there is evidence of left-axis deviation.

ber 23. Electrocardiograms repeated on several occasions when the pulse rate was slow showed a 2:1 heart block. On November 23, the white-cell count increased to 32,500 and x-ray therapy of the heart was again given as well as on three subsequent occasions at weekly intervals. Three

white-cell count would affect the heart block and pulse. Consequently this treatment was given on February 4, 17 and 25 and March 8. As a result, the white-cell count dropped to 7800, where it remained until May 24, when it was 11,800. During this time, even though the white-cell count was di-

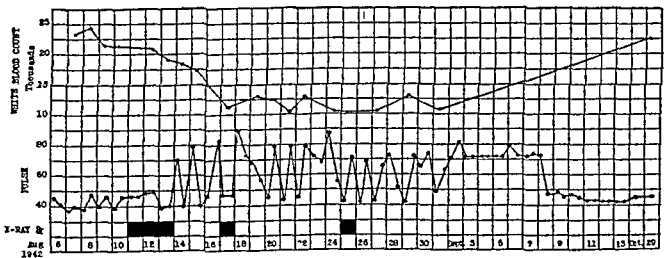


FIGURE 2. Effect of X-ray Therapy of the Heart on the Pulse and White-Cell Count.

The black blocks represent the dates on which x-ray therapy of the heart was given. The pulse rate had previously varied from 36 to 48 for a period of five months.

days later the pulse rose to 72 for 5 minutes and then dropped to 44. X-ray therapy of the heart was repeated on December 1, 7 and 15 (Fig. 3). The white-cell count dropped to 19,800 on the last date and the pulse was 72 for several minutes. From December 17 to January 18, 1943, it ranged from 72 to 80 except for a 3-day period in December when it was 48. The blood pressure was 200/100. Subsequently

minished to normal, the pulse remained at 48, although on two occasions after exertion it rose to 72 for a few minutes. The blood pressure remained at 200/100 until May 24, when it rose to 270/90. The patient had felt faint with considerable abdominal distress and was acutely conscious of her heart beat. She stated she had felt best after she had had x-ray therapy of the heart and when the heart was not in block.

On May 29, the blood pressure rose to 300/100 and a right hemiplegia occurred. The patient became unconscious and died within 3 hours.

COMMENT

This was an interesting case, with hypertension and with severe and frequent headaches for many years, for which the patient took a great deal of Pyramidon. In March, 1941, it was found that she had myelogenous leukemia, which readily responded to spray x-ray therapy to the trunk anteriorly and posteriorly. A year later, the patient developed a 2:1 heart block that persisted for five months. It was believed that this block was due to a leukemic infiltration or nodule involving the bundle of His. Consequently, x-ray therapy was directed to the heart and the heart

tases,^{2,3} and cardiac arrhythmias may occur in tumors of the heart.^{4,5}

The cause of the leukemia in this case is unknown, although one son, a physician, believed that it was due to the long-continued use of large doses of Pyramidon. A report in relation to Pyramidon was made by Delore and Borgomano,⁶ who observed leukemia in a worker who for five years had extracted Pyramidon with benzene; the disease may have been due to the Pyramidon rather than to the benzene.

SUMMARY

This paper reports the case of a woman who had hypertension for twenty years and leukemia for two years. For five months she had a 2:1 heart block that was believed to have been due to a

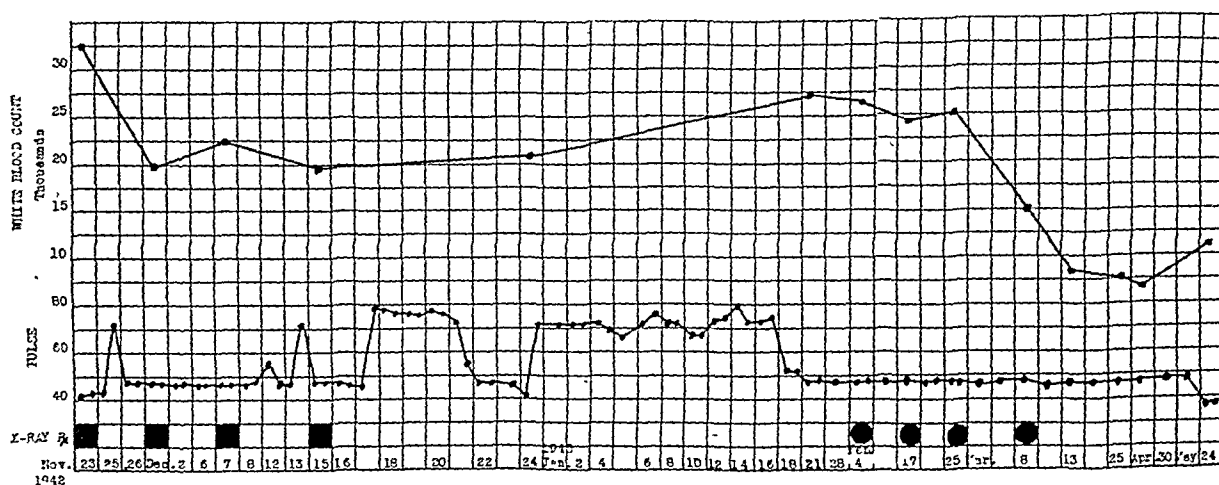


FIGURE 3. Effect of X-ray Therapy of the Heart and Trunk on the Pulse and White-Cell Count.

The black blocks represent the dates on which x-ray therapy of the heart was given; the black circles, the corresponding dates for x-ray therapy of the trunk. For ten weeks previously, the pulse had varied from 42 to 48.

block disappeared intermittently for seventeen days and then persistently for seven days. When the heart block reappeared and persisted again for over two months, x-ray therapy was applied to the heart, and again the heart block disappeared intermittently for a month and then persistently for twenty-three days. The heart block then reappeared, and a month later when the white-cell count was 24,900 x-ray therapy was given to the trunk. Although the white-cell count remained at a normal level for three months, the heart block persisted. It is known that heart block may appear and disappear without obvious cause. The results in this case, however, strongly suggest that x-ray therapy applied directly over the heart, by its effect on a leukemic infiltration of the heart, which involved the conduction mechanism, caused the heart block, which had been present for five months, to disappear on two occasions.

Leukemic infiltrations in the myocardium are not uncommon and rarely lead to alteration in the mechanism of the heart action.¹ Leukemic infiltrations may, however, produce, besides diffuse infiltrations, definite nodules resembling tumor metas-

leukemic nodule or infiltration involving the bundle of His. X-ray therapy applied to the cardiac area was followed by a disappearance of the heart block for several days on two occasions. Finally, on a third occasion when the white-cell count was elevated and the heart was blocked, x-ray therapy applied to the trunk did not cause the heart block to disappear even though the white-cell count was reduced to normal.

It is suggested that x-ray therapy of the heart caused the heart block to disappear by its effect on a possible leukemic infiltration of the heart that involved the conduction mechanism.

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MEDICAL PROGRESS

SPONTANEOUS, THREATENED AND HABITUAL ABORTION: THEIR PATHOGENESIS AND TREATMENT*

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BOSTON

SPONTANEOUS abortion, together with its intimately related syndromes of threatened and habitual abortion, is a frequent and therefore important complication of pregnancy. A voluminous literature not only attests to these facts but also emphasizes the general biologic complexity of the condition.

That man is not the only species subject to this complication of pregnancy is shown by studies on embryonic pathology in mammals (Corner¹). Thus, the domestic sow shows a fairly constant ovular mortality of approximately 30 per cent, as judged by the discrepancy between the number of ovulated ova — based on counts of corpora lutea — and the number of, such potentially fertilizable ova that reach full term as viable living fetuses. A similar situation obtains in laboratory animals such as the rat, rabbit and ferret. A comparable ovular mortality has been postulated in domestic animals, such as cows and mares, that ordinarily liberate but one ovum at the height of estrus. It has long been known that a normal pregnancy does not necessarily result from the single mating of a known fertile pair of such domestic animals. Such failures, according to Gowan,² may amount to 20 to 25 per cent in beef and dairy cattle, and are ascribed to disasters that may overtake the ovum at any time from its ovulation through fertilization and subsequent development. Approximately one third of the 30 per cent defective ova in animals that produce litters, constituting about 10 per cent of the total number of ova thus liberated, reach a stage in their development that coincides with a clinically recognizable pregnancy. The other two thirds, or 20 per cent of all ovulated ova, may fail to become fertilized, to undergo segmentation or to implant. Thus, the 10 per cent that do implant and that develop to a variable degree but ultimately die before full term are closely analogous to the 10 per cent (approximately) of human pregnancies that end in abortion.

Rock³ in a review published in this journal in 1940 summarized all the essential aspects of abortion. It is the purpose of the present article to

stress the pathogenesis of spontaneous abortion and to summarize the recent literature with respect to the treatment of the theoretically preventable forms of this condition, namely, threatened and habitual abortion. Stated differently, it is an attempt to trace the various pathologic stages leading up to a spontaneous abortion and to determine what proportion of such abortions are treatable, at what stage in their development such treatment must necessarily be instituted to save the pregnancy and what constitutes modern methods of treatment.

It is apparent that any spontaneous abortion goes through various stages, including the threat to abort as evidenced by bleeding and uterine cramps, and progresses ultimately to an inevitable abortion that may be either complete or incomplete. It is furthermore evident that during this stage, when the patient is threatening to abort, it may be difficult or impossible to determine clinically whether or not the pregnancy can be salvaged. Hence, all threatened abortions must, in the absence of more precise clinical signs, be considered salvageable until proved otherwise. A certain proportion of such abortions, however, subside without any specific treatment other than bed rest and mild sedation, the remainder being completed. The latter pregnancies are therefore the only ones that yield information about the causes of abortion. In a large proportion of cases, pathological examination of such abortuses gives a definite clue as to the cause of the abortion. My⁴ analysis of 1000 abortuses forms the basis for the statements on the pathogenesis of spontaneous abortions.

It is evident that any rational treatment of threatened or habitual abortion must be directed toward saving the pregnancies that are fundamentally salvageable when the patient is first seen, even though the physician does not at that time know whether or not such a pregnancy can be saved. For this reason, the results of the treatment of threatened and spontaneous abortion reported in the literature should be interpreted in the light of the foregoing, for it must be stressed that a certain proportion of such patients will not abort anyway and a certain proportion will abort no matter what the treatment. The percentage of successfully treated threatened and habitual abortions must therefore consist of the group of pregnancies that

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would not have aborted anyway, in addition to those that are salvageable when the patient is first seen. This percentage would be ascertainable if the various factors were known. Unfortunately, at the present time not all such factors are known, or at least agreed on, by the various authors writing on the subject.

INCIDENCE

Spontaneous Abortion

It is generally agreed by most authors that by a conservative estimate 25 per cent of pregnancies end in abortion of induced, therapeutic or spontaneous origin.³ The latter cause accounts for one third of the total group, or approximately 8 per cent of all pregnancies. Among other authors, Mason⁶ and Silbernagel and Burt⁶ place this figure at 6 and 13 per cent, respectively. I⁷ have examined pathologically all the abortuses from a large private obstetric practice in Boston over a period of six years, and have found the incidence of spontaneous abortion to be 10.6 per cent of the 1150 cases of full-term pregnancy and spontaneous abortion combined. If the cases of therapeutic abortion, hydatidiform mole and ectopic pregnancy are included in the total, the proportion of the total number of obstetric cases ending in spontaneous abortion becomes 10.4 per cent. In a report on the treatment of habitual abortion with vitamin E authorized by the Council of Pharmacy and Chemistry of the American Medical Association I⁸ summarized the findings of various American authors (Plass, Brunner, Newton, Simmons and Kopp) and concluded that 9.8 per cent of all pregnancies terminate in spontaneous abortion. It seems fair, in view of the foregoing data, to assume that approximately 10 per cent of all pregnancies abort spontaneously.

Threatened Abortion

In order to evaluate properly the results of the treatment of threatened abortion, it is necessary for the physicians who treat it to have a uniform concept of what the condition is. Unfortunately, not all therapeutic reports in the literature appear to define threatened abortion in the same terms. For example, Mason⁵ and Soule⁹ consider hemorrhage or uterine cramps or both to constitute a threat to abort, whereas Silbernagel and Burt⁶ state that a threatened abortion is always accompanied by uterine bleeding, either with or without uterine cramps. Rutherford¹⁰ required that the patient pass an amount of blood by vagina—excluding cervical and vaginal lesions—sufficient to make a stain 5 cm. in diameter on a vulvar pad before the case was classed as a threatened abortion. It seems by a priori reasoning that the threat to abort is less serious if the patient merely has uterine cramps instead of uterine bleeding, either with or without cramps. Hence, the results of any therapy in the first group may reasonably be expected to be better than those in the second group.

The incidence of threatened abortion is variable, as one would expect from such variations in the concept of the condition. It occurred in 0.94 per cent of 24,289 pregnancies at the New York Hospital (Javert and Stander¹¹) over a period of eight and a third years. Paine¹² states that 3.8 per cent of the patients at the Evangeline Booth Hospital in Boston threatened to abort, a figure that is in essential agreement with that of Rutherford¹⁰ of 4.0 per cent for the Boston Lying-in Hospital.

Since all patients who ultimately abort must necessarily threaten to abort for a variable period before they complete the process, the true incidence of threatened abortion must be at least as great as the incidence of spontaneous abortion. In the light of this fact, and considering an accepted incidence of 10 per cent for spontaneous abortion, the incidence of threatened abortion appears to be surprisingly low. This discrepancy is rationalized only when one considers the incidence of threatened abortion in private practice. Silbernagel and Burt⁶ state that 140 (16 per cent) of their 870 private obstetric patients threatened to abort, whereas 10.9 per cent of Mason's⁵ private patients did so. The only explanation for this discrepancy between the figures of large obstetric hospitals and those of private obstetric practitioners lies in the fact that private patients consult their physicians much earlier in pregnancy than do a comparable group of clinic patients. Hence, many of the potential clinic patients who are only two to three months pregnant have threatened to abort, and indeed have carried out that threat before coming to the hospital for their initial visit. That this assumption is true is shown by the frequency with which clinic patients give a history of having had a previous abortion at home and having consulted their physician or hospital, if at all, only because of continued bleeding due to incompleteness of the abortion.

If it is difficult to obtain uniformity of opinion on what constitutes a threatened abortion and on how frequently the condition actually occurs, it is even more difficult to obtain figures that are in uniform agreement regarding the prognosis of the pregnancy when once it threatens to abort. Irving¹¹ states that over half the patients who threaten to abort ultimately go to term and deliver normal babies. Other authors, however, are by no means so sanguine in their outlook. Thus, Javert and Stander¹¹ found that 100 per cent of their untreated threatened aborters aborted. Silbernagel and Burt⁶ found that only 6 per cent of their untreated threatened aborters went to term, whereas 24 per cent of Rutherford's¹⁰ 91 cases failed to abort.* Parish¹⁴ and Falls and his co-workers¹⁵ are in rela-

*It must be pointed out, however, that endometrial biopsies were taken from the lower uterine segment of these patients in an attempt to determine the state of the endometrium and thus gain some idea of the inevitability of the abortion. The concept back of this study was based on my continued observation over a number of years that all abortuses show a marked degree of decidual sinusoidal thrombosis, with resultant decidual necrosis and hemorrhage. It was argued that, with the presence of this triad of pathologic signs, the prognosis for a pregnancy was poor—even though the ovum had not yet aborted.

tively close agreement that 57 and 39 per cent, respectively, of their control cases of threatened abortions go to term. Walsh, in discussing Paine's¹² paper, makes a general statement that nearly half the threatened abortions are saved. Bach and Winkler,¹⁶ according to an abstract in the *Journal of the American Medical Association*,¹⁷ state that 50 (65 per cent) of their 74 control cases of threatened abortion continued to term. Some doubt may be cast on this figure, because in another abstract¹⁸ of the same article the title is slightly different and includes cases of habitual as well as threatened abortion.

It appears that such a variation in the prognosis of untreated threatened abortion will have to be rationalized and an agreement reached on what the true prognosis of untreated threatened abortion is before the real worth of various specific therapies for this condition can be evaluated.

Habitual Abortion

This condition, according to the report of the Council on Pharmacy and Chemistry of the American Medical Association,⁸ "is defined by Bishop as premature delivery on more than one occasion before the fifth month of gestation not due to discoverable disease, organic cause or artificial induction." This concept is not entirely in accord with mine, since it is possible to have recurrent spontaneous abortion caused by discoverable disease and an organic factor, as will be shown later in the section on pathogenesis. A more rational approach to the problem would be to consider a true habitual aborter as one who "has had at least two consecutive abortions."⁸ If this last definition is further clarified to include the phrase "two consecutive spontaneous abortions," I shall be in perfect accord with it.

The incidence of habitual abortion may be expressed in terms of its proportion of total pregnancies or as a simple percentage of all spontaneous abortions. Thus, the incidence given by Bishop⁸ is 0.41 per cent of a series of 2687 pregnancies, whereas Malpas's¹⁰ comparable figure is 1.0 per cent. In Javert and Stander's¹¹ series of 1648 abortions admitted to the New York Hospital, 59 (3.6 per cent) of the patients gave a history of having had three or more abortions. It is not evident from the latter author's data what proportion of either the habitual or the total series of abortions were induced. If one admits that 35 per cent of all abortions are spontaneous in origin (see above) and assumes that all these 59 cases were true spontaneously recurrent abortions, 9.8 per cent of the total number of Javert and Stander's spontaneous abortions were due to recurrent causes. Actually, the proportion of habitual abortions in all spontaneous abortions probably lies somewhere between the 3.6 and 9.8 per cent. Similarly, if Bishop's⁸ figure of 0.41 per cent as representing the absolute incidence of

habitual abortion in pregnancy is used and it is realized that 10 per cent of all pregnancies abort spontaneously, the proportion of spontaneous abortions that are due to recurrent factors is 4.1 per cent. These figures are in general agreement with the conclusion in the report of the Council on Pharmacy and Chemistry,⁸ based on Whitehouse's²⁰ data, "Although the diagnosis of repeated abortion might have been made in from 4.5 to 6.8 per cent of the cases considered in this analysis, it seems likely that at least 2.9 per cent of the women were liable to repeated abortion and possible that 7.7 per cent may have been subject to the probability of abortion as great as 0.84."

PATHOGENESIS

Threatened Abortion

There are no definite statements in the literature concerning the underlying pathologic anatomy of this condition. It seems logical, however, to assume that the endometrium shows the same fundamental picture as in spontaneous abortion, namely, thrombosis of decidual sinusoids with resultant necrosis of and hemorrhage into the decidua. The degree of this process is probably not so marked in threatened as in spontaneous abortion.

These assumptions on my part are based on observations made on the endometrium (decidua) of therapeutically removed early pregnant uteri at the Boston Lying-in Hospital and the Free Hospital for Women. Beneath the developing placentas of such pregnancies one almost invariably encounters a small area of necrotic decidua with its associated thrombosed sinusoids. Thus, there exists even in anatomically normal pregnancies a mechanism that may lead to bleeding from the placental site and hence cause the clinical syndrome of threatened abortion.

The cause of this disturbance in the placental site of a normal pregnancy, which is beyond the scope of this paper, is probably the continual encroachment of the growing placenta on the endometrium of the placental site. It is probably a matter of chance, therefore, whether the necrosis is extensive enough to cause bleeding and, if so, whether the blood will escape into the vagina and thus become clinically evident. It becomes apparent, in the light of these observations, that not all uterine bleeding necessarily means an inevitable abortion; nor, on the other hand, does it surprise one that a significant percentage of spontaneous abortions may produce anatomically normal ova that are salvageable if proper treatment is instituted in time.

Spontaneous Abortion

The data in the subsequent section are a summary of an analysis of 1000 spont.

miscarriages examined pathologically at the Boston Lying-in Hospital during a six-year period. The original data were published by me⁴ in collaboration with Sheldon in 1943.

During this study it became apparent that two main factors were operating to produce a spontaneous abortion, namely, those traceable to defects or abnormalities of the ovum and those due to maternal causes. In the former category were 617 abortuses, or 61.7 per cent of the series, whereas the remaining 383, or 38.3 per cent, were in the latter category.

It is obvious that, no matter how detailed is the pathological examination of the abortus or how perfect is the clinical history, — which many histories in this series were not, — this approach to the problem of spontaneous abortion is subject to error. Some of the interpretations, therefore, may be open to question. This is so if only for the reason that the pathological study of the abortus alone leaves out one, if not the most important, aspect of the problem — the pathological examination of the uterus. Furthermore, these studies are not correlated with any associated endocrinologic studies of the patient — another important aspect of the problem. Be that as it may, they furnish some clue to the essential problem in the pathogenesis and treatment of spontaneous abortion; namely, what sort of ova spontaneously abort and how many of them could theoretically have been salvaged when the patient was first seen by the physician.

Ovular factors. The largest single group of causes of spontaneous abortion is that which results in the production of a blighted or pathologic ovum: that is, one in which the embryo is absent or extremely defective. In this category were 489 abortuses, or 48.9 per cent of the total number. This over-all classification does not take into account the bitter controversy that has raged for years regarding the factor or factors that cause these ova ultimately to become pathologic. It is not within the scope of this article to decide whether all these ova were defective from the beginning (germ-plasm defects) or whether one or more environmental factors acted on a normal fertilized ovum, causing it to become pathologic. Suffice it to say that my studies with Rock²¹ have shown that intrinsically pathologic human ova exist soon after implantation. Four such specimens, together with an abnormally implanted but otherwise normal ovum, have been recovered from surgically removed uteri prior to the first missed menstrual period. Each of these specimens was yielded by patients who had previously had several normal pregnancies. Their fertility, therefore, had been established and general abnormalities of uterine environment ruled out.

Aside from the fact that this group of blighted ova constitutes almost half the abortuses examined, an additional fact of importance is that approximately two thirds of these ova showed variable

degrees of hydatidiform degeneration of their chorionic villi.²² In rare cases such ova, tending to abort in their tenth week of gestation, for reasons not understood, remain in the uterus and become a classic hydatidiform mole. This fact must be kept in mind in treating any case of threatened abortion, for the physician may unwittingly convert an inevitable abortion of such a pathologic ovum into a true hydatidiform mole. The probability of such an occurrence is remote, but it is nevertheless possible. One such patient, who had been treated for threatened abortion for the previous six months by a local physician, came to the Boston Lying-in Hospital and was delivered of a hydatidiform mole. The chance that this mole might have developed spontaneously cannot, of course, be ruled out.

In the series of abortuses under consideration, there were 32 (3.2 per cent) that showed localized anomalies — usually of the nervous system. That such anomalies are not incompatible with a full-term delivery and even some degree of extrauterine life cannot be gainsaid. The incidence of such anomalies was, however, four times as great as is the incidence of such anomalies in full-term deliveries at the Boston Lying-in Hospital. With these facts in mind, it is well for the physician treating threatened abortion to remember the additional possibility of bringing to term a monster that would otherwise have aborted.

Javert and Stander,¹¹ in commenting on this problem, state that although infants born of mothers who have threatened to abort are not necessarily malformed, the tendency may be greater than otherwise. Thus, Kotz et al.,²³ quoted by Javert and Stander,¹¹ gives 4.9 per cent as the percentage of malformed fetuses born to a group of mothers treated for threatened abortion, whereas these authors¹¹ found that in 27,000 deliveries at the New York Hospital only 2.95 per cent of the infants were so afflicted. Greenhill²⁴ found the average incidence of fetal abnormalities in twenty-six clinics to be only 0.94 per cent. The same author, however, found that forty clinics showed an average of 2.75 per cent fetal abnormalities in cases of placenta previa. In the light of these various data, it appears that treated cases of threatened abortion run an increased risk of producing a malformed infant, although Shute,²⁵ quoted by Silbernagel and Burt,⁶ denies that such a mother runs an increased risk.

Various abnormalities of the placenta, all associated with normal embryos, constitute 9.6 per cent of these 1000 abortuses. Various derangements of placental formation and function are found in this group, but the commonest ones are the circumvallate placenta (4.5 per cent), hypoplasia of the placenta (2.0 per cent) and the so-called "Breus's mole" (1.9 per cent) — the latter a normal placenta in which the maternal blood has clotted, thereby causing fetal death.

though two thirds of these fetuses were macerated at the time of the abortion, nearly half were living when the symptoms or signs or both that brought the patient to the physician began. This fact is determined by knowing the date on which such symptoms or signs began and by calculating the

TABLE 1. Classification of Cases with Anatomically Normal Ova.

CLASSIFICATION	No. of Cases
Anatomically normal ova without disease:	227
Fetus macerated	146
Fetus living	81
Acute chorionitis, consistent with spontaneous premature rupture of membranes:	14
Fetus macerated	9
Fetus living	5
Positive Hinton and Wassermann tests (syphilis probably not responsible for abortion)	3
Infarction of placenta, extensive (all fetuses macerated)	13
Toxemia of pregnancy:	5
Fetus macerated	3
Fetus living	2
Trauma	
Internal:	
Two successive endometrial biopsies on sterility patient not known to be pregnant	1
Exploratory laparotomy	1
Intrauterine injection of lipiodol 7 weeks prior to last menstrual period	1
External:	
Automobile accident (a bona fide cause of this abortion) .	1
Total	266

menstrual age of the fetus from the classic tables of Streeter.²⁷ By this means it is possible to determine whether the fetus was younger or older than the duration of pregnancy when bleeding first began. If the former was true, the fetus was dead prior to the onset of bleeding, whereas if the latter proved to be the case, the fetus was living after the onset of bleeding. It becomes evident, therefore, that two thirds of these pregnancies with normal ova were theoretically capable of being salvaged instead of merely the apparent one third that showed living fetuses at the time of the abortion.

Considering all types of abortuses in which there was a normal, albeit sometimes a dead, fetus at the time of abortion, it is apparent from these figures that 47.9 per cent of this series of 1000 cases could be so classified. Furthermore, if one applies to this group the rough theoretical salvage rate of two thirds of such cases, one finds that one third of all spontaneous abortions contain a normal living fetus at the time the patient is first seen. This is perhaps erring in favor of the therapists, although the figure is not far from the actual truth. It is from such a group of cases, together with those of threatened abortion that would not have aborted anyway, that one must draw the group of successfully treated threatened aborters. It is difficult to see how a successful case could come from any other group unless, perchance, it came from the group about which there might be differences of opinion whether it really contained bona fide cases of threatened abortion.

Habitual Abortion

Few data exist on the pathogenesis of habitual abortion other than those contained in such a series

as that discussed above in the section on spontaneous abortion. What data exist in my series can be summarized by saying that the causes of habitual abortion are apparently as varied as those resulting in a chance or single spontaneous abortion. Correlated with the clinical definition of the disease, as one resulting in two successive spontaneous abortions, is the repetition of pathologically identical or similar causes in successive abortuses. Thus, in a series of 14 patients, each of whom had two successive spontaneous abortions that were examined pathologically, each pair of abortuses appeared to have occurred following the same or similar causes. A habitual aborter, therefore, is a patient who tends to repeat a given clinicopathologic syndrome rather than to experience it only once.

Because of this fact, the problem of treating habitual abortion has at least some justification for being approached optimistically by the physician. If the patient is a known habitual aborter, it is at least theoretically possible to determine something of the probable cause or causes of future abortions and to set about treating the condition at the time of conception — an advantage not possessed by the physician treating a threatened abortion which may, from the beginning of signs and symptoms, be inevitable.

TREATMENT

This section concerns the treatment of threatened and habitual abortion only, since, once the abortion has become inevitable or is in the process of taking place, treatment becomes a matter of emptying the uterus as quickly and as safely as possible.

The problems of treating threatened abortion and habitual abortion seem to be essentially different. In the former instance, efforts are directed at stopping the uterine bleeding and associated cramps, when present. In the latter, one seeks to prevent the various and often quite diverse factors that have contributed to the previous abnormal pregnancy. Thus, the treatment of the one is essentially an emergency procedure, whereas that of the other is, or should be, an elective procedure, preferably begun before conception. Actually, when one examines the results of treatment as shown in the various published series of cases (Table 2), it appears that the same method of treatment may be equally successful whether the case be one of threatened or of habitual abortion. The only difference appears to be the stage in the pregnancy at which the treatment was started and the dosages of therapeutic agents used.

Table 2 presents the data in series of cases of threatened and habitual abortion reported by various authors, including the methods of treatment and the results. It is impossible in such a table to give details of treatment, for which the reader is referred to the original articles. In the cases listed under habitual abortion there had been

two or more successive abortions, so far as could be determined, cases stated as having had only one previous abortion being excluded. Some authors, however, did not give the number of previous abortions, and their cases may or may not have been those of true habitual abortion. The numbers of

Anhydro-hydroxy-progesterone (Pregneninolone — Ciba, Praxinone — Schering). The oral dosage in threatened abortion is 10 to 100 mg. daily in one or divided doses for a period of three days to several weeks; that in habitual abortion is 10 mg. twice weekly. This synthetic progestational principle is said by Krohn and Harris² to be one sixth as effective as progesterone. It is not, however, identical in its action on the uterus (Burge and Holloway²⁸). Progesterone

TABLE 2. Summary of Data on the Treatment of Threatened and Habitual Abortions.

SENIOR AUTHOR	THREATENED ABORTION		HABITUAL ABORTION		TREATMENT
	NO. OF CASES TREATED	NO. (PERCENTAGE) SUCCESSFULLY TREATED	NO. OF CASES TREATED	NO. (PERCENTAGE) SUCCESSFULLY TREATED	
Burge ²⁸ (1941)	3	1 (33)			Anhydro-hydroxy-progesterone
Buxton ²⁹ (1940)			5*	4 (80)	Progesterone
Campbell ³⁰ (1940)			13*	11 (85)	Progesterone
Huber ³⁰ (1940)			15*	14 (93)	Corpus luteum hormone
Singleton ³⁰ (1940)			3*	2 (67)	Vitamin K (young grasses)
Collins ³¹ (1940)	24	21 (88)	12	9 (75)	Vitamin E (wheat-germ oil), progesterone and thyroid
Currie ³² (1937)	15	14 (93)	37†	35 (95)	Vitamin E (wheat-germ oil)
Davis ³³ (1942)	30	17 (57)	16	8 (50)	Anhydro-hydroxy-progesterone or progesterone and thyroid
Elden ³⁴ (1938)			8	6 (75)	Progesterone
Ehrhardt ³⁵ (1936)			2	2 (100)	Placental extract
Falls ³⁶ (1936)			41	34 (83)	Progestin
Falls ³⁶ (1942)	217	189 (83)	59	51 (86)	Lutein
	234	206 (88)	63	58 (94)	As above
	61	53 (87)	55	51 (93)	As above
Hamblen ³⁷ (1941)	1	1 (100)			Etirole glucuronide, anterior-pituitary-like hormone and progesterone
Hamblen ³⁷ (1941)			5*	1 (20)	Progesterone, etirole, anterior-pituitary-like hormone and thyroid
Hurst ³⁸ (1918)			3*	2 (67)	Corpus luteum extract
Javert ³⁹ (1943)	10	8 (80)	14*	13 (93)	Vitamins C and K, thyroid, progesterone and various minerals
Kane ³⁹ (1936)			40	36 (90)	Proluton, thyroid and sodium iodide
Karnaky ⁴⁰ (1942)	16	16 (100)			Stilbestrol
Kotz ⁴¹ (1941)	139	64 (46)	42	37 (88)	Progesterone
Krohn ⁴¹ (1935)	11	9 (82)	8	5 (63)	Progestin
Krohn ⁴² (1941)	39	32 (82)	11	10 (91)	Anhydro-hydroxy progesterone and barbiturates
Lubin ⁴³ (1941)	35	13 (37)	7*	5 (71)	Vitamin E (synthetic)
Malpas ⁴⁴ (1938)			7*	2 (29)	Vitamin E (wheat-germ oil)
Malpas ⁴⁴ (1938)			4*	2 (50)	Progestin
			33*	20 (61)	Organic arsenicals
Mason ⁴⁴ (1938)			3*	3 (100)	Anterior pituitary-like hormone (pregnancy urine extract)
Mason ⁴⁵ (1942)	34	30 (88)	17	15 (88)	Progesterone
McCorr ⁴⁵ (1937)			3*	3 (100)	Progestin
Olson ⁴⁶ (1943)	167	91 (55)			Various (opiates, barbiturates, atropine, vitamin E, progesterone and thyroid)
Parker ⁴⁷ (1941)			1‡	1 (100)	Vitamin E (wheat germ oil) and progesterone
Rosenfeld ⁴⁸ (1938)			20	19 (95)	Pregnancy serum (500 cc weekly throughout pregnancy)
Schneider ⁴⁹ (1942)	24	12 (50)	16*	16 (100)	Estrogens or progesterone
Schneider ⁵⁰ (1942)	2	2 (100)			Estrogens or progesterone
Shute ⁵¹ (1942)	46	35 (76)			Vitamin E (wheat-germ oil)
Soule ⁵² (1941)	16	12 (75)			Anhydro-hydroxy-progesterone or progesterone, or both, and thyroid
Stahler ⁵² (1941)			14*	13 (93)	Vitamin E (synthetic) and progesterone
Vogt-Möller ⁵³ (1933)			20	17 (85)	Vitamin E (wheat-germ oil)
Vogt-Möller ⁵⁴ (1936)			56	38 (68)	Vitamin E (wheat-germ oil)
Watson ⁵⁵ (1936)	15	11 (73)	28*	21 (75)	Vitamin E (wheat-germ oil)

*Stated to have had two or more previous successive abortions.

†Stated to have had two or more previous abortions, but not whether successive.

‡Eight previous successive abortions, and hence worthy of inclusion, even though only a single case.

treated cases in the reports including a statement of two or more successive previous abortions are followed by an asterisk.

The therapeutic agents listed in Table 2 deserve comment, and the following is a brief outline of the dosages and the methods of administration.

is antagonistic to Pituitrin, whereas anhydro-hydroxy-progesterone is not.

Wheat-germ oil (vitamin E). The oral dosage is 30 to 45 cc in the first twenty-four hours in divided doses, and 4 to 6 cc. daily thereafter until the eighth calendar month (Collins⁵).

Synthetic vitamin E (Alphatocopherol — Squibb). The oral dosage is up to 30 mg. daily and up to 240 mg. monthly in divided doses.

Thyroid. The oral dosage is 6 to 30 mg. (1/10 to 1/2 gr.) two to three times daily.

Progesterone. Doses varying from 1/25 rabbit unit to 10 mg. have been given intramuscularly. The average dose for bleeding is 2 to 10 mg. Soule,⁹ whereas the prophylactic dosage is 1 mg. every three or four days for a variable length of time but occasionally through the sixth month.

Diethylstilbestrol. The dosage in threatened abortion (Karnaky¹⁰) is 25 mg. injected into the anterior wall of the cervix, followed by 5.5 mg. every fifteen minutes as long as pain persists. When the latter disappears, 10 mg. is given orally every hour for six doses and then 5 mg. every hour for six doses. Following subsidence of pain and bleeding, 10 mg. is given by mouth daily until the eighth month. In habitual abortion, 10 mg. is given in a like manner as soon as pregnancy is diagnosed and is continued until the seventh month.

Lutein. This is an aqueous extract of corpus luteum (Hynson, Westcott and Dunning) whose exact composition is unknown and at present has not been completely bioassayed. Its effective strength is said by Falls¹⁵ to be such that 1 cc. is equivalent to 1/10 unit of progesterone. In threatened abortion, Falls and his collaborators inject 3 cc. intramuscularly every four hours during active bleeding and cramping, in addition to absolute bed rest. After symptoms of bleeding and pain have subsided, 3 cc. is given daily for five to seven days and then 3 cc. twice a week until viability is reached. For habitual abortion, these authors inject 3 cc. intramuscularly twice a week.

Threatened Abortion

It is evident from Table 2 that several hundred cases of threatened abortion have been treated in a variety of ways. There is a total of nine series^{5, 15, 23, 32, 40, 42, 43, 51, 55} containing 15 or more cases in which only one specific therapeutic agent was used. The latter varied from diethylstilbestrol through natural and synthetic vitamin E to preparations of corpus luteum.

These various specific agents may not be quite so diverse in their action on the pregnant uterus as appears at first glance. Thus, the metabolism of the estrogens and that of progesterone are closely correlated, as shown by the work of Smith and Smith.⁵⁶⁻⁵⁸ A practical illustration of this correlation is the method by which Schneider^{49, 50} treats his cases of threatened abortion: estrogen and pregnanediol levels are determined and the patient is given the hormone that is shown to be abnormally low. Also, the role of vitamin E in its essential relation to normal pregnancy is not yet well understood: Stähler and Kaiser,⁵² Stähler and Pehl⁵⁹ and Bach and Winkler¹⁶ cite evidence for the relation between vitamin E (synthetic tocopherols) and progesterone, whereas Shute⁶¹ speaks of the imbalance between vitamin E and estrogens. A relation between vitamin E and iron assimilation by the fetus is indicated by the work of Simmonds, Becker and McCollum.⁶⁰ These workers ascribe fetal death in rats deficient in vitamin E to a crisis in iron assimilation that is obviated by giving vitamin E in adequate amounts at the beginning of pregnancy.

These specific agents for the treatment of threatened abortion are often used in various combinations, either with or without the addition of thyroid. The role played by the latter in pregnancy is not fully understood. That it is important, however,

is shown by the increase in the abortion rate in so-called "goiter areas" (Hamblen,⁶¹ 1943). With the adequate use of thyroid in such areas, there is a reduction in the abortion rate.

Other specific substances, such as the so-called "antihemorrhage" vitamins C and K, have recently been used in the treatment of threatened abortion by Javert and Stander.¹¹ In a high proportion of these authors' cases the use of these substances is predicated on the demonstrably low values of the substances themselves or of their essential end product.

The treatment of threatened abortion is centered on the problem of stopping hemorrhage and quieting the uterus. For this purpose some gestational principle is often used. Hamblen,⁶¹ in a recent review article, thus summarizes the status of this phase of the therapeutic problem:

Numerous reports have cited the efficacy of progestin in preventing abortion. Progestin often has received credit for success when the effects of adjuvant measures, such as thyroid substance, bed rest, limitation of sexual and other activities and so forth, have not been evaluated. We have not been impressed particularly with progesterone therapy in these conditions. Our percentage of successfully treated patients has not been as high as those of some other investigators, although the dosages were comparable or larger. When pregnant women show definite evidence of deficiency in the gestational principles, — that is, decreased pregnanediol values of the urine, — even the most intensive progesterone therapy fails to prevent abortion.

Although apparently patients with low levels of pregnanediol excretion often abort and therapeutic efforts may fail to raise the levels of this substance by progesterone administration, the administration of some potent corpus-luteum preparation, preferably progesterone, seems indicated in cases of threatened abortion with uterine cramps, since this is probably the most effective way of stopping such signs and symptoms if the abortion is not inevitable. Concerning progesterone versus other derivatives of the corpus luteum, Macht⁶² cites evidence that an aqueous extract of the latter, Lutein (Hynson, Westcott and Dunning) is a potent preparation, 1 cc. of which is equivalent to 0.1 mg. of progesterone. It must be realized, however, as Buxton²⁹ states, that there are so many variables in progesterone metabolism and excretion that pregnanediol assays cannot indicate the degree of gestational activity.

Ideally, of course, it would be desirable to know in advance whether or not a threatened abortion is inevitable. Since this is impossible, efforts are necessarily directed at saving the third of spontaneous abortions that theoretically can be saved, even though this entails treating the remainder, which are inevitable in spite of treatment. If it is possible to determine, as does Schneider,^{49, 50} which of the ovarian hormones is low in a case of threatened abortion, the low one should be administered. Otherwise, it seems well to treat the patient by some

form of corpus-luteum preparation, vitamins E, C and K and thyroid, this treatment being correlated with a program of so-called "nutritional adequacy," as advocated by Javert and Stander.¹¹

That the treatment of threatened abortion is unsatisfactory at best is indicated by the variety of its causes and the present diversity of its treatment. Elucidation of these complex etiologic factors and evaluation of one or several specific therapeutic agents in various combinations await the study of large series of cases by investigators who will use the combined talents of the obstetrician, the endocrinologist and the embryologic pathologist. Until this time comes, the treatment of threatened abortion and its closely related syndrome, habitual abortion, rests on the physician's practical judgment aided by empiric uses of more or less specific substances whose action is not fully understood at the present time.

Habitual Abortion

The foregoing remarks are applicable in general to the problem of the treatment of habitual abortion. This condition differs from chance abortion in that the same etiologic factor tends to be repeated in two or more successive abortions. Such a recurrent factor is often the same as the chance or isolated factor causing a single abortion.

Treatment should begin prior to conception, because the genesis of many abortions is laid during the time before the first missed menstrual period. The same over-all treatment is indicated as is advocated above for threatened abortion, because of the present lack of more specific therapeutic knowledge. The use of progesterone or some other potent corpus-luteum derivative is indicated before bleeding and cramping begin, because of its effect on the pregestational endometrium and the latter's effect, in turn, on the ovum — even before its implantation.

Vitamin E, judging from the literature, has an important effect on the favorable outcome of pregnancy in cases of habitual abortion — this in spite of the fact that the average human dietary cannot be shown to be deficient in vitamin E. Bacharach,¹² in 1940, summarized several relatively large series of true habitual abortions reported by other authors and showed that vitamin E apparently supplied the specific factor, so that patients with two, three and four previous abortions had a 75, 73 and 79 per cent chance, respectively, of a successful pregnancy. The rate of spontaneous cure in such cases if untreated, according to Maltas,¹³ would have been 62, 28 and 7 per cent, respectively.

In contrast to these relatively hopeful data are the conclusions of the report of the Council on Pharmacy and Chemistry of the American Medical Association,³ also published in 1940, which used some of the same data reviewed by Bacharach.¹² This report states that vitamin E cannot as yet be accepted owing to lack of convincing evidence,

because the diagnosis of habitual abortion is open to question in these cases, because of the variation in dosage, and because not enough is known about the spontaneous cure rate in habitual abortion. Nevertheless, in my opinion vitamin E should be used because it appears to offer great hope in salvaging pregnancies that would otherwise habitually abort.

CONCLUSIONS

Threatened abortion occurs in at least 16 per cent of all pregnancies.

Spontaneous abortion occurs in approximately 10 per cent of all pregnancies.

Habitual abortion constitutes approximately 4 per cent of all spontaneous abortions.

Approximately 40 per cent of threatened abortions do not abort regardless of the treatment employed.

Approximately 60 per cent of threatened abortions abort if untreated.

On the basis of a series of 1000 cases examined embryologically and pathologically, approximately one third of spontaneous abortions are theoretically capable of being salvaged at the time the patient is first seen by the physician.

In view of the three preceding conclusions, approximately 60 per cent of threatened abortions under adequate treatment may fail to abort.

Threatened abortion should be treated by some potent corpus-luteum preparation or, if estrogens are demonstrably low, by the administration of these substances. These hormones should be supplemented by vitamins E, C and K and thyroid, in conjunction with a program of so-called "nutritional adequacy."

Habitual abortion should be treated in the same manner as is recommended for threatened abortion, except that treatment should begin prior to or coincident with conception.

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in case some of my remarks seem to be elementary at times.

"A sixty-five-year-old housewife entered the hospital because of abdominal pain." When one sees a patient or examines a protocol like this, which is essentially the same thing, I think one gets an immediate impression. I make a mental note that the patient was in the decade of life when on the whole carcinoma is most frequent, and that the patient was a woman, and therefore the possibility of disease of the pelvic viscera must be considered later.

If we can believe the history it is perfectly obvious that there was no immediate antecedent history that had anything to do with this attack. It was a sudden, acute abdominal attack. The light lunch obviously had nothing to do with it. She had severe abdominal cramps, which were obviously due to painful peristalsis, and immediate vomiting. What is the significance of these two symptoms? First, of course, by far the most frequent cause of abdominal pain with vomiting and cramps is some form of acute gastroenteritis, gastrointestinal "flu" if you like, or some functional disturbance. In other words, it would, up to that point, explain everything perhaps, and the diagnostician's chief care is to differentiate the functional disturbance of that sort, which is obviously not surgical, and an acute condition in the abdomen of a surgical nature. That is always the thing that should come to the mind of the local physician when he sees such a patient.

As to the bowel movement, it may be presumed that she was somewhat constipated and that the lower colon and rectosigmoid were full of feces when she came in, and with some stimulation of peristalsis she had three formed stools, which means the normal movement of the lower bowel, and the last one semiformed.

The vomiting is interesting. She vomited nine times with distressing retching every time. When the stomach and intestine are affected by a functional disturbance there may not be very much pain. There is apt to be vomiting and diarrhea, but once the intestine is empty that is apt to be the end of it, although the intestinal diarrhea may go on. Here is a woman who nine times had repeated retching and vomiting. We are not told whether the vomitus or the gastric contents contained bile or blood or material suggestive of jejunal contents, but we assume, inasmuch as we are not told these things, that it did not contain anything significant. I think it was one of the Mayo group who once said, among many other wise things, that the stomach was the alarm clock of the physical economy. The stomach is apt to reject its contents, and vomiting to set in, in all sorts of conditions — acute gastritis or any acute condition within the abdomen. As you well know, the emotions may cause vomiting, or it may occur at the beginning of infectious disease or with disturbance of the internal ear or a brain

tumor, and so it goes. In other words vomiting must never be considered as necessarily or even probably indicative of trouble in the stomach, although that is a frequent cause. So my impression here is definite — that this vomiting was of a reflex nature due to some insult to the peritoneum of the abdominal viscera below the stomach and probably had nothing at all to do with the stomach.

Evidently this patient was not used to gritting her teeth, and waiting and suffering in silence. She sent for a doctor quite promptly. She undoubtedly was an intelligent person. From here on there is mentioned a number of times the type and degree of peristalsis noted. Some of the gentlemen here may have devoted themselves to the study of peristalsis. Personally, I do not believe that much significance can be attached to the determination of peristalsis, except very broadly; if we examine the abdomen and find absent peristalsis we may assume that in all probability the situation of paralytic ileus exists. The prototype and usual cause is peritonitis, unless there be some toxic cause. The other is extreme peristalsis with a tinkling sound, which we hear in the early stages of acute mechanical obstruction. Between these extremes one cannot tell much about the significance of peristalsis, but evidently the group that studied this case did think there was a good deal in it, very likely something I do not realize.

Of course the degree of tenderness is extremely important but there was no localized tenderness, and no spasm, and therefore, we can confidently rule out peritonitis. Certainly we can rule out acute perforative peritonitis. Acute perforation of a hollow viscus would give exquisite localized pain, exquisite localized tenderness and boardlike spasm and rigidity — a very different thing from what we have here. The question arises, Of what significance was this tenderness? Was there any peritoneal insult? Hardly. I simply remind you of the fact that if any of you have happened to be unfortunate enough to be seasick, and perhaps have vomited nine times, with retching, you know that the belly becomes quite tender, so I do not believe that this tenderness was important; but we can say that there was no perforative peritonitis. "Abdominal tenderness became more marked, so that any but the most superficial abdominal palpation caused marked pain referred to the midepigastrium." Again we should like to know how much tenderness there was, but again we may assume that there was no marked spasm related to it. So that it does not seem to me significant. The reference of the pain to the epigastrium is extremely interesting, of course, and must be of great importance. Anatomically speaking, we think of the organs that are situated in the epigastrium shall not bore you with enumeration — the stomach, pylorus, duodenum and forth cover so

remember that the pancreas is situated there. It is an organ that must always be considered in any acute abdominal situation. The symptoms of acute pancreatitis, the typical ones, are very characteristic; yet many a case of pancreatitis is quite obscure from a diagnostic point of view. So let us remember the pancreas.

What is the likeliest cause of the pain in the epigastrium? As we know, pain due to spasm of the small intestine as contrasted with painful peristalsis of the large intestine, is apt to be referred to the region above the umbilicus, and in the large intestine is apt to be referred to the hypogastrium, below the umbilicus, and that, as you well know, is because the sympathetic pathways from the intestine are related to certain metameres of the body — thus pain in the small intestine is associated with pain sensations referred to the distribution of the seventh, eighth, ninth and tenth dorsal nerves in the epigastrium. That is a general statement and a useful one, but of course it must be mentioned that it is frequently violated.

"There was no pain in the back, shoulder or scapula." That statement refers undoubtedly to the absence of symptoms that might have been caused by injury to the phrenic area. Also, absence of pain in the back suggests that the gall bladder was not involved.

The vague mass that was palpable we must take as something that could not be identified; its actual existence was not certain.

This patient had a very discriminating and keen physician to attend her. The notes that he makes here are those of an experienced man who has seen this type of case. One-sixth of a grain of morphine after he made the examination was necessary, and the proper treatment. One-sixth of a grain could hardly mask any important symptoms. We know that she got through the night very well indeed. As to the propriety of having her go through the night, if I were a beneficent dictator, I should advise that any patient with acute abdominal pain and vomiting in which there is any doubt whether something more than a functional disturbance exists should go to a hospital. But perhaps that is too much to expect, and certainly the course of this case justified her being kept where she was. We surgeons know that the possibilities of acute abdominal pain and vomiting are so great that we should like to have had her under hospital observation where interferences could have been carried out if necessary. The night is quite long for a patient with acute abdominal pain.

"She had one small, liquid, pinkish bowel movement." That is extremely interesting and important; undoubtedly the color was due to blood. Something caused bleeding into the gastrointestinal tract. The most probable thing would be an ulcer. We do not know whether she had previously had occult blood in the stools, but here definite gross

blood appeared, which suggests ulceration. But bear in mind that it also suggests interference with the circulation in the intestine somewhere, or strangulation, or acute passive congestion, with a little leakage into the intestinal loop. Indeed, that is extremely important.

It is perfectly evident that the doctor became convinced that the disturbance in the upper abdomen should be under surgical observation.

It is interesting that the patient had had anemia for years and had had liver therapy, but it is obvious that she did not have pernicious anemia. It is just possible that she had had for years some lesion in the bowel that had been leaking a little bit, not causing enough bleeding to be observed but enough to cause anemia; possibly there was a connection between that and the present condition.

This patient had had a laparotomy and uterine suspension thirty-three years before entry. I should like to call to your attention that whenever the surgeon sees an abdominal scar he attributes a great deal of importance to it. In the first place, whatever the condition was for which she was operated on, it may have recurred, and one particularly thinks of carcinoma. The second point is that there may be a condition in the abdominal wound itself that may be the cause of the present symptoms. Of course I refer to a weakened wound with interstitial hernia, which is evident to the examiner. The third point, and in this case much the most significant, is that the operation may have resulted in adhesions, which cause some sort of band that may be the cause of the symptoms. Thirty-three years is a long time for that. It would depend a great deal on the character of the operation. It says "uterine suspension," I suppose of the modified Watkins's type. It might have been an attachment of the fundus of the uterus to the abdominal wall, which makes a long pulled-out band that is just the kind of thing which loops of small intestine insinuate themselves around and give obstructive symptoms, but I am surprised that that could have occurred so long after the operation. It is possible that a hysterectomy was done at that time. Hysterectomy in the hands of the average surgeon in those days was not the same as it is now. There was no satisfactory effort made to repair the pelvic floor, and there was quite a long area, running from the pelvic brim across to the cervix, where adhesions could easily form and produce acute intestinal obstruction, owing to strangulation by a band due to the adhesions.

The physical examination does not mention whether there was vomiting after the initial nine spells, which would be interesting to know. There was little real spasm. Again we have no suggestion of peritonitis, and I call your attention to the fact that the typical syndrome of acute, complete, intestinal obstruction was absent, that is to say, pain, obstipation, distention and vomiting. There

was pain, and there had been vomiting, but there was no persistent obstipation or distention. So we do not have the inevitable syndrome of symptoms that necessitate a diagnosis of acute intestinal obstruction. Still there may be intestinal obstruction because all these elements of the syndrome may not be present.

"Peristalsis was almost entirely absent." The intestine got tired trying to pass things along, and that suggests a little bit the possibility of peritonitis. "Palpation anywhere in the abdomen gave rise to pain in the epigastrium." That would not be so in pancreatitis; as a rule, palpation would have to be more or less over the region of the pancreas if the pain were due to pancreatitis. This does suggest to me, however, that intestinal coils on palpation of the abdomen were pushed about from one part to the other, making traction on the root of the mesentery, which would cause pain in the epigastrium. There was no definite spasm or tenderness over the abdomen, and with acute pancreatitis there should be definite tenderness and spasm, although not the boardlike rigidity of the perforated viscus. No vaginal or rectal examination is mentioned. Of course they were done, and we may assume that they were negative.

"Examination of the blood showed a white-cell count of 17,300, with 86 per cent neutrophils." That is an indeterminate degree of leukocytosis. I call your attention to the fact that there may be a certain amount of hemoconcentration, which increases the white-cell count to a certain extent.

Then we come to the x-ray examination, and we might glance at the films. The small intestine normally contains little if any gas. It is almost always completely filled with fluid. In obstruction there is gas, and we must be able to differentiate small intestine and large intestine. There you see quite plainly the valvulae conniventes close together—so different from the haustra of the large intestine. The diameter of the bowel is distinctly increased, not markedly so. I am not sure whether this other loop is small intestine or large intestine. That may be normal large intestine. The one loop of distended small intestine almost certainly means obstruction. Another point is that there is no gas under the diaphragm, which, if this were taken in the standing position, would be evidence against perforation.

An operation was performed two hours after admission. I call your attention to the fact that probably we cannot, from this printed protocol, get a satisfactory idea of the patient's condition. From it I learn that she had a good night and came in without having had further vomiting, that the blood pressure fell a little and that the white-cell count was slightly elevated; the picture as given is not that of a very sick woman. The history, however, is extremely significant and it is perfectly clear that the experienced men who saw her made

up their minds that it was an acute condition of a surgical nature. Let me remind you—I have it underlined here—that the most important factor was not the exact condition existing here, but whether it was a surgical emergency; in other words, whether there was a condition that might have been treated expectantly along medical lines, or whether she had to be explored. I am not going to enumerate all the causes of acute episodes like this in the abdomen with symptoms of at least partial obstruction, perhaps complete obstruction, but I am going to bring to your attention, of course, the question of Meckel's diverticulum. It must be remembered that, that being a congenital anomaly, it would be rather strange to have a Meckel's diverticulum become adherent late in life and form a band that became strangulated. If attached to the umbilicus it would have caused symptoms earlier. It is still a possibility. Another condition that I shall rule out from lack of antecedent history and from lack of x-ray confirmation is obstruction from a gallstone that had ulcerated into the intestine, although, let me say immediately, a large cholesterol gallstone can ulcerate through to the duodenum and a phlegmatic patient often gives no antecedent history, and the x-ray may not show it.

Then there is volvulus, but that does not appeal to me. There is intussusception. Intussusception, of course, is almost practically confined, except for a few cases that have been described, to the period of life before five years; most of them occur before one year of age. Intussusception of the terminal ileum into the cecum is the usual rule. But there is a form occurring in the adult that usually appears in the small intestine and is invariably due to the presence of a tumor, and in my experience usually a nonmalignant tumor, a lipoma or fibromyoma of the small intestine. The tumor gets caught in a peristaltic wave and gets drawn into the distal bowel; it is pulled along by peristalsis and forms a true intussusception that can relieve itself readily and may occur again and again. The first attack may be significant. If that occurred here it would have caused obstruction accompanied by acute passive congestion, with leakage of blood into the bowel. Moreover, we might link it up with the moderate degree of anemia for a considerable period, because such a tumor may have given rise to leakage from time to time, although I do not believe that that is important.

Pancreatitis, I am going to remind you, is always a possibility, but the lack of marked tenderness in the epigastrium and pain in the back, the very sudden onset, which is not characteristic of pancreatitis, and the failure to get any antecedent history to suggest it practically rule out pancreatitis.

I see no cause for considering thrombosis. There is nothing to suggest arterial mesenteric em

There is another point to stress, and I am perfectly certain that it was done here, and that is that one never fails, when confronted with a case like this, to examine with the greatest of care the region of inguinal and femoral hernias. In a woman, femoral hernia, especially in an adipose woman, may be so small as to be indistinguishable. The pain of hernia may not be referred to the site of the hernia but to the epigastrium because of the pull on the mesentery of the bowel which is attached there. I know of two cases in which, because of the combination of an ultramodest patient and a diffident physician, the site of femoral hernia was not examined and therefore operation was delayed, with resulting exitus.

So far as operation is concerned, the anesthesia was probably spinal, although some people think that the inhibition of the sympathetic nerves leading to increased peristalsis produced by spinal anesthesia might be harmful in intestinal obstruction. Local anesthesia and gas would be fairly satisfactory. If a general anesthetic were used, especially ether, we would surely pass a stomach tube first and keep it in place during anesthesia. There is nothing more fatal than the vomiting that occurs under ether anesthesia in cases of intestinal obstruction. I presume a paramedian incision was made, starting at the umbilicus.

DR. BENJAMIN CASTLEMAN: Would you like to state your first choice?

DR. CHEEVER: Intussusception due to tumor, probably benign, of the jejunum.

DR. ARTHUR W. ALLEN: I should like to compliment Dr. Cheever on his masterly discussion of this patient. He has covered the situation with great thoroughness.

This patient happened to be the widow of a physician who was a colleague of mine in World War I. I have known her a good many years. I had never seen her professionally, but I had known that she had a hard time keeping a normal weight and that she had a good deal of gastrointestinal difficulty requiring special diet—iron, liver and so forth.

Dr. John T. Quinby is the man who saw her first and realized that she was an ill woman. He talked to me about her on the telephone about seven o'clock in the evening, and I suggested that it would be all right to give her a little relief with 1/6 gr. of morphine and that if she did not get better from the "ptomaine poisoning" which she was sure she had, I would come in to see her. I did see her about nine-thirty that night and could not, for the life of me, bring myself to think that she represented an acute abdominal emergency. The lack of high-pitched peristalsis, the fact that the vomitus at that time was nothing but undigested food, with no evidence of intestinal contents, the repeated stools, the reference of her pain to the epigastrium, with actually more tenderness in the

epigastrium than elsewhere, made me believe that my second choice, after acute gastrointestinal upset, was pancreatitis.

In defense of Dr. Quinby I might say that we tried to get her into the hospital, but there were no beds; so the best we could do was to get a nurse and Dr. Quinby stayed with the patient through the night, keeping his eye on her. I thought that was as adequate as having her in the hospital, where we should undoubtedly have kept her under observation much the same way.

The next morning, at six o'clock, it was obvious to us that she was still ill, and finally the Admitting Office decided we could have a bed in the Emergency Ward. We got her in and immediately had this x-ray film made, which, of course, clinched the diagnosis. But before this film was made and before Dr. Quinby told me there was blood in the stool that she passed during the night, I thought that this woman had a medical disease, not a surgical belly; that is how close we came to missing it.

CLINICAL DIAGNOSIS

Intestinal obstruction, small bowel.

DR. CHEEVER'S DIAGNOSES

Intestinal obstruction.

Intussusception due to tumor, probably benign, of jejunum.

ANATOMICAL DIAGNOSES

Intestinal obstruction.

Infarction of small intestine due to adhesive band.

PATHOLOGICAL DISCUSSION

DR. ALLEN: At operation we found intestinal obstruction due to a band that was running from the region of the right upper quadrant across the terminal ileum, very close to the cecum, but far enough away to allow the entire mesentery of the small bowel to rotate around it. There was an enormous amount of dead terminal ileum due to thrombosis of the vessels that had become occluded mechanically by the torsion. The band ran down to the region of the old suspension—a very small band, not more than 2 mm. in diameter.

I was confronted with the problem of how much small intestine she could spare. She had had a hard time getting on with what she had been born with. So I started at the terminal ileum and removed the bowel up to a point where I thought there was some chance for the rest of it to come back, taking out 71 cm., which is an appreciable length. We then observed the other 100 cm. or so of small bowel that was involved, which made a fairly satisfactory return. I had to gamble that complete circulation would be restored to the latter segment, since I knew that, had I taken it out, she would certainly

have suffered from a deficiency state. Anastomosis between the ileum and the cecum was done, and she made a pleasant and uneventful convalescence.

DR. CHEEVER: There are two things I should like to say. The first is to emphasize the impossibility, in a case of intestinal obstruction, of deciding, with any certainty, whether or not strangulation exists. I think Dr. Allen will bear me out in this — until the matter has reached the final stage there are certain things one cannot be sure of. The other thing, which I say with the utmost sincerity, is that this patient was fortunate that she fell into the hands of someone who knew what he was doing. When I learned that it was a good friend of mine, I was much pleased, but to spare his blushes I should not say so.

CASE 30262

PRESENTATION OF CASE

First admission. A sixty-three-year-old watchman entered the hospital because of gnawing abdominal pain.

The patient had been in apparent good health until nine months before entry, when he noticed frequent attacks of heartburn, which came on a few hours after eating and were relieved by soda and food. Three months before entry he was seen in the Out Patient Department, where a gastrointestinal series showed a small crater in the pylorus. He was placed on a six-meal bland diet and tincture of belladonna. In the course of the next two months he experienced considerable relief, and x-ray films showed definite evidence of healing. A gastric analysis showed no free acid in the fasting specimen and only 38 units after histamine injection. During the month prior to admission the patient had recurrence of the heartburn and lack of appetite.

Physical examination on admission showed a well-developed, well-nourished, but pale man. The heart, lungs and abdomen were normal.

The blood pressure was 120 systolic, 75 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 4,600,000, with 12 gm. of hemoglobin. The white-cell count was 8500, with 67 per cent neutrophils. The urine was normal. A blood Hinton test was negative. The stools were guaiac negative. A gastrointestinal series (three and a half months after the first studies) showed a large crater above the angle of the stomach, slightly toward the anterior wall. Below this point there appeared to be one or more smaller craters.

The patient was given a gastric diet and atropine. After two weeks on this regime repeat x-ray studies showed the large ulcer to be approximately the same size as it was in the previous examination. Accord-

ingly, a subtotal gastrectomy and posterior antiperistaltic Hofmeister anastomosis were performed. The pathological examination showed peptic ulcers without any evidence of malignant disease. Postoperatively the patient did well, and he was discharged home on the thirty-seventh hospital day.

Final admission (one month later). Following discharge the patient remained well until six days before readmission, when he had two chills without fever, felt ill and went to bed. Two days later he vomited whitish, questionably bile-stained material. About that time he noted the onset of jaundice. Subsequently, the stools became clay colored, and the urine dark. At no time did he experience pain or have fever. He had had no previous jaundice.

Physical examination showed a moderate degree of jaundice. There were tenderness and voluntary spasm in the right upper quadrant. On deep inspiration the liver edge was palpable 5 cm. below the costal margin in the anterior axillary line. Examination was otherwise negative.

The blood pressure was 95 systolic, 60 diastolic. The temperature was 98.6°F., the pulse 85, and the respirations 20.

Examination of the blood showed a white-cell count of 5200. The hemoglobin was 82 per cent. The stools were clay-colored, with brown streaking and a ++ guaiac test. The urine was normal. The blood nonprotein nitrogen was 35 mg., and the protein 5.2 gm. per 100 cc. The blood chloride was 98 milliequiv. per liter. The van den Bergh was 10.3 mg. direct, and 14.6 mg. indirect. A film taken after one swallow of barium showed the barium to pass readily through the stoma into the nondilated efferent loop. The spleen was slightly enlarged. A film of the abdomen was normal.

The patient was given intravenous fluids. The jaundice increased. In the course of the next six days, the direct van den Bergh rose to 18.6 mg. per 100 cc., and the indirect to 24.4 mg. A bromsulfalein test revealed 100 per cent retention.

On the sixth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WYMAN RICHARDSON: I have no idea what a "posterior antiperistaltic Hofmeister anastomosis" is. It might be important in this case. Presumably this patient had transfusions at that time, but I want to know definitely whether he did. That is a fair question, I believe.

DR. BENJAMIN CASTLEMAN: He was given two transfusions.

DR. RICHARDSON: That is enough.

I take it that the two chills he had were real, otherwise they would not be put in the abstract.

I should also like to know whether he had ever had any fever. I should prefer that he had fever during the second admission.

DR. CASTLEMAN: Here is the chart.

DR. RICHARDSON: He had a temperature of 101°F. by rectum for one day.

"The van den Bergh was 10.3 mg. direct, and 14.6 mg. indirect." As I have said many times before, the latter is misleading. The 14.6 mg. is the total bilirubin. One has to subtract 10.3 from 14.6 to get what we ordinarily consider the indirect. In other words, the van den Bergh test showed that two thirds the bilirubin was demonstrated by the direct method, which of course is suggestive evidence of obstructive jaundice. The bromsulphalein test showed 100 per cent retention, which anyone would have predicted in a patient with this degree of jaundice. There is no point in doing this determination in the presence of severe jaundice.

I should like to make a comment or two about the laboratory findings before I go on to differential diagnosis. The first is about the blood. In this case a blood smear would have been helpful. If it had shown some abnormal lymphocytes, suggesting mononucleosis, I do not believe that this would have been detected on the surgical service and probably not always on the medical service. This finding would be of some differential importance, suggesting infectious hepatitis. Another thing I want to comment on is the total protein of 5.2 gm. If that was an accurate determination it is definitely low.

In regard to differential diagnosis, I am going to take up only three possibilities: silent stone in the common duct; adhesions or distortion due to ulcer or possibly postoperative inflammation resulting in obstruction to the common duct; and acute infectious hepatitis.

I do not believe this patient had stones. My chief reason for this statement is that the combination of gallstones and ulcer in the same patient is almost unheard of. If anyone has heard of that combination I should be glad to have him speak up. It is a striking thing that the ulcer habitus and the gallstone habitus are quite different, and I do not believe that I have ever seen the two diseases in the same patient. There are other features about the case that are against stone. He had had no previous attacks of pain, but of course one can never rule out stone on that basis.

Now what about the question of jaundice due to ulcer? One can have jaundice due to ulcer in the region of the ampulla, or one might have a considerable inflammatory reaction around an ulcer that was near the ampulla, but one would not get it from ulcer in or above the pylorus. There is no mention or suggestion of ulcer below the pylorus, so I think that that can be ruled out.

That brings up the question of an inflammatory postoperative reaction. Just why there should have been a considerable amount of inflammatory reaction in the region of the common duct, I am not sure; but it would seem possible as a result of the rather complicated gastric surgery that went on. The sudden onset with chills is very much opposed

to that diagnosis, however. I should expect a gradual onset with jaundice and nothing else — a rather slow progression of severe and intense jaundice after a period of a good many weeks. This was rather sudden in onset, with chills and possibly fever and then severe jaundice, an apparent rapid increase in the size of the liver and possibly splenomegaly by x-ray examination.

I therefore think that the evidence is in favor of infectious hepatitis. If so, what was the cause of it? One would have at least to bring up the possibility that it was caused by the transfusion that was received at the previous operation. My diagnosis is infectious hepatitis possibly secondary to transfusion.

I want to say one more thing, which is certainly true whether I am right or wrong about the diagnosis. There was no particular hurry about operating on this patient. It seems to me that he was operated on too quickly. He should have been kept in bed and watched for a while. Now that we know that we can protect against prothrombin lack, there is not too great a risk. It is less of a risk to be sure that one does not operate on a patient with a sick liver due to hepatitis.

DR. CASTLEMAN: How do you tie up the transfusion with the infectious hepatitis?

DR. RICHARDSON: I was thinking of the modern theory that transfusions from donors who have had jaundice due to hepatitis within a year may be able to transmit the disease to the recipient. There have been some deaths. I believe that it has occurred in all situations involving the injection of human serum. The thought is that the disease is due to a virus.

DR. EARLE M. CHAPMAN: I want to comment on Dr. Richardson's second possibility — a post-operative inflammation about the common duct or head of the pancreas — to explain this man's jaundice. When visiting on the West Medical Service recently I saw four patients with the same pattern of jaundice following surgery for duodenal ulcer, and yet the surgeons insisted that there was no relation between the two. Two of these patients recovered gradually. The chief finding in both was marked tenderness in the epigastrium, suggesting an inflammatory reaction.

CLINICAL DIAGNOSIS

Obstructive jaundice.

DR. RICHARDSON'S DIAGNOSIS

Infectious hepatitis, possibly due to transfusion.

ANATOMICAL DIAGNOSES

Intrahepatic cholangitic biliary cirrhosis.
Acute hemorrhagic pancreatitis, with fat necrosis.
Icterus.
Bile neph.

Operation: subtotal gastrectomy with posterior gastrojejunostomy.

Bronchopneumonia, diffuse.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At operation the surgeon found the peritoneal cavity remarkably free of adhesions.

present at operation ten days before because it would have been easily seen. The manipulation of the gall bladder at operation possibly forced some bile into the pancreatic duct, thus producing the pancreatitis.

Microscopically the liver presented a very unusual process. There was widespread parenchymal

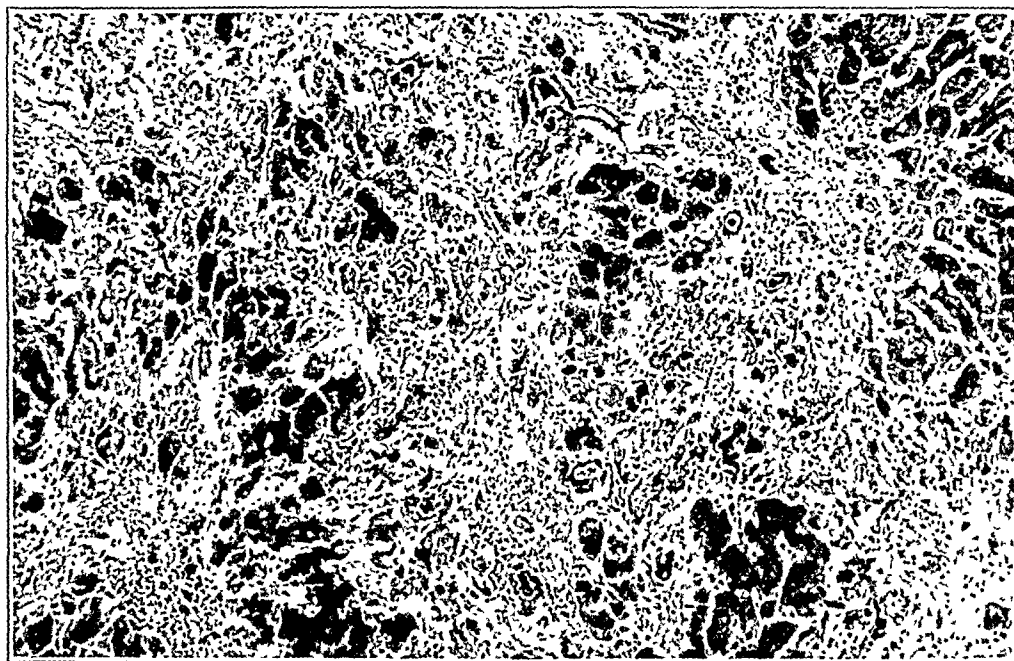


FIGURE 1. Photomicrograph of Liver, Showing Widespread Liver-Cell Damage.

There was a small amount of bile-stained fluid. There was no dilatation of the duodenum or of the afferent loop. The pancreas was normal in size and consistence. By pressure on the gall bladder he was able to empty it into the duodenum and to aspirate thin greenish bile from an inlying nasal tube. He palpated the entire common duct and found no evidence of stone, tumor or other obstruction. The liver was yellowish-green, tense and firm. Since no obstruction was found, nothing further was done.

Following operation the patient continued to do poorly, became drowsy and disoriented and died on the eleventh postoperative day.

The autopsy showed a normal-sized liver, which was definitely green and slightly firmer than normal. The gall bladder appeared normal. The common duct was perhaps slightly thickened, but normal in size, patent and free from stones. In the region of the head of the pancreas we found a mass measuring 8 cm. in diameter; this was a bit fluctuant and, when cut into, appeared to be an acute hemorrhagic affair. Scattered all over the surface were areas of fat necrosis. There is no question that this was acute pancreatitis. This mass could not have been

destruction involving from half to two-thirds of each liver lobule, which was replaced by granulation tissue infiltrated with lymphocytes and large numbers of polymorphonuclear cells (Fig. 1). There was bile stasis in the tiny bile canaliculi, which were tremendously distended and filled with so-called "bile thrombi" (Fig. 2). This is somewhat similar to the appearance that one sees with an extrahepatic obstructive biliary type of cirrhosis. In this case we were unable to find any extrahepatic biliary obstruction. Karsner,* in a recent review of the literature on hepatic cirrhosis, has used the term "intrahepatic cholangitic biliary cirrhosis," a diagnosis that I believe can be applied to this case. It is an intrahepatic obstructive and infectious process. The lesion, if we go back to when the patient had his first chill, was about twenty-three or twenty-four days old, and microscopically the picture is consistent with that age. One might ask, What is the relation between the liver disease and the acute pancreatitis? Of course, if the acute pancreatitis had occurred first we might assume that it had ob-

*Karsner, H. T. Morphology and pathogenesis of hepatic cirrhosis. *Am J. Clin. Path.* 13:569-606, 1943.

structed the papilla and that the infection had spread up the lymphatics into the liver. The absence

overlooked at operation, rules out this possibility. A PHYSICIAN: Was a blood culture taken?

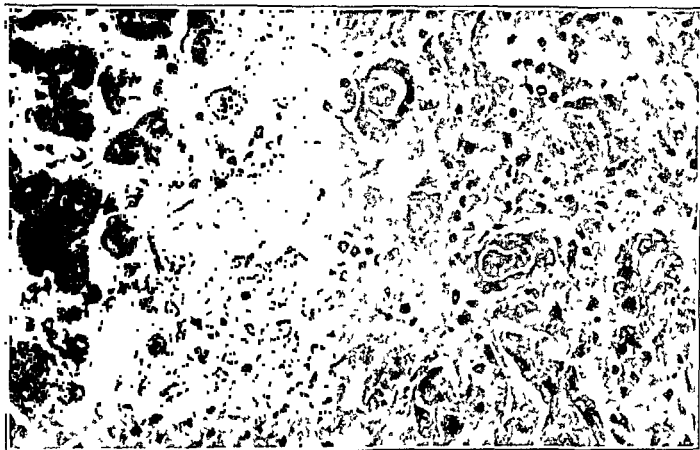


FIGURE 2. Photomicrograph at a Higher Magnification, Showing Bile Thrombi and Inflammatory Reaction.

of dilatation of the common duct, both at operation and at autopsy, as well as the fact that it seems unlikely that the pancreatitis could have been

DR. CASTLEMAN: The post-mortem culture showed a nonhemolytic streptococcus, which may have been a contaminant.

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

RH TYPING SERUM

Rh typing serum is now available for all who need it. This should be welcome news to the obstetrician and to the physician or surgeon administering transfusions, who appreciate the importance of this new blood type and have been concerned because of the lack of diagnostic serum. For the doctor who is not aware of the dangers of Rh incompatibility, the letter regarding the practical aspects of this subject, published elsewhere in this issue of the *Journal*, should be informative.

Except for the important obstetric complications, the sequelae resulting from the repeated trans-

fusions of Rh- recipients with Rh+ blood are obviously of greater concern to physicians in the armed forces than to those in civilian practice. For the former often uses multiple transfusions in the treatment of hemorrhage, shock, blast or burn injury, or chronic infection, and the one man in seven who is Rh- deserves the protection that is offered by this special typing of blood.

The early and, until-recently, the chief handicap to differentiation of Rh+ and Rh- red cells was the scarcity of potent, rapidly active serum. The supply of such material was dependent on the identification of high-titered anti-Rh agglutinins in the blood of the rare woman who built up these antibodies during and maintained them after the birth of one or more infants with erythroblastosis fetalis. Statistically, such an event occurs about once in more than 5000 deliveries. Even if such women were willing and able to donate a pint of blood frequently, the supply of anti-Rh serum from this source alone would fall far short of meeting the usual demand of civilian hospitals and the expanded needs of military establishments. It was therefore necessary to develop a method whereby larger amounts of Rh typing serum are available for immediate use. This project is explained in the letter referred to above, and co-operation of all physicians will ensure its success, thus benefiting chiefly the members of the armed forces at the moment, and everyone after the present emergency passes.

After the war it seems likely that Rh typing will assume even greater significance than it does at present. Certainly, whole blood and resuspended red cells will be readily available and will probably be used freely. The Rh- men returning to civilian life who received one or more transfusions of whole blood during the war may have developed an appreciable titer of Rh agglutinins if Rh+ blood was used, and on being again transfused, severe hemolytic reactions may occur following the injection of Rh+ red cells. Furthermore, the current civilian needs for Rh typing will not diminish. For these reasons, proper Rh typing serum will be required in abundance. The present project offers promise of meeting the need.

THE "OFFENSIVE" ODOR OF GARLIC AND ONIONS

A FEW years ago the American medical profession was greatly amused, if not much enlightened, by two articles concerning garlic breath that appeared in the *Journal of the American Medical Association*.^{1,2} A recent issue of the *American Review of Soviet Medicine*³ calls attention to a series of scientific investigations on the possible beneficial effects of the vapors of these alliaceous plants when used as bactericides or as phytoncides (plant bactericides).

The therapeutic possibilities of garlic have, in the past, been studied and utilized to a varying degree even in this country and in Great Britain. It has been used in the treatment of infectious diseases such as pneumonia,⁴ as an antihelminthic⁵ and in the treatment of hypertension.⁶ Observations have been made on the bactericidal effect of garlic and onions in vitro against many bacteria,⁷ including *Mycobacterium leprae*.⁸ A systematic study was also reported on the physiologic effects of garlic and of derived substances.⁹ Some of these were found to be highly toxic, whereas others, which are noxious for bacteria or other parasites, are apparently nontoxic and thus have therapeutic possibilities.

The Soviet investigators summarized the results of many experiments concerning the phytoncidal activity of alliaceous plants. They found that extremely small amounts of a paste of freshly macerated onion, garlic or similar plants emit enough phytoncide to kill all exposed unicellular organisms within one to five minutes. They found no protozoa that were resistant to the phytoncide of garlic or onions. They also demonstrated that free-living infusoria and certain flagellates are affected. In certain paramecia, they noted first an apparent stimulation of motility, followed by specific morphologic changes that continued after all motility had ceased. Other investigations indicated that large concentrations of these vapors introduced into animals by inhalation caused a rather pronounced stimulation of the wandering cells of the connective tissue but no parenchymatous changes in the organs.

The Russian workers went on farther, applying these plant phytoncides in the treatment of in-

fected wounds. Gratifying results were obtained in many cases of delayed healing, particularly amputated stumps in which there was considerable purulent inflammation of the wound. Regeneration of tissues proceeded rapidly in spite of the frequent dressings required by the treatment. All the clinical results, however, were not favorable. In some cases, epithelization stopped suddenly after a few treatments, and in others, there was an increase in granulation tissue and a lack of epithelization in other parts of the wound.

These findings may serve to intensify the interest in finding new remedial agents derived from living plants, including micro-organisms. The practical results are well exemplified in the great advances that followed the discovery of gramicidin and penicillin. The finding of new and effective substances leads, in turn, to identification of the active principles with a view to defining the chemical structure of the agents responsible for the various beneficial activities, as well as those associated with toxic properties. Eventually this should lead to synthesis of similar or related chemical compounds having the optimum therapeutic activity and the least injurious effects.

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CORRESPONDENCE

RH TYPING SERUM

To the Editor: In 1940, Landsteiner and Wiener discovered a new antigenic substance in the blood—the Rh factor—present in 87 per cent of the white population and absent in 13 per cent. At first it was thought to have no practical or clinical importance. It was soon demonstrated by Levine and by Wiener, however, that Rh—persons (those lacking this Rh agglutino-gen) might, under certain circumstances, develop immune antibodies against the Rh factor and suffer serious consequences from the action of such anti-Rh agglutinins.

Abundant evidence has been collected by now to show that anti-Rh agglutinins may be developed in Rh—males and females as the result of one or more transfusions with Rh+ blood, and in women by repeated pregnancies involving an Rh+ fetus (this blood type being inherited as a dominant characteristic from the father).

Recognized intragroup transfusion reactions due to Rh incompatibility have apparently been quite rare in civilian practice. This does not imply that Rh- persons who receive Rh+ blood fail to develop antibodies. On the contrary, data from the Blood Grouping Laboratory in Boston suggest that many such recipients develop weak agglutinins. Subsequent transfusion reactions are fairly mild unless numerous transfusions are given and agglutinins increase in strength. Probably the most important reason for the failure to note a higher percentage of hemolytic transfusion reactions of this type is that multiple transfusions are the exception in civilian practice, more than 95 per cent of the transfusions being single infusions of blood. In contrast to this, in the treatment of members of the armed forces, multiple transfusions are exceedingly common, and therefore transfusion reactions in the 13 per cent of the population who are Rh- are quite likely to become more frequent and severe, thus interfering with benefit from the procedure, with speed of convalescence and even with eventual recovery. This has been borne out by the published statistics.

Because of the increasing availability of plasma and whole blood, and the attempt to diminish maternal mortality due to hemorrhage and puerperal sepsis, transfusions are now given to patients on obstetric services much oftener than in days past. In contrast to the experience with medical or surgical cases, a first transfusion of Rh+ blood to an Rh- mother who has been sensitized by pregnancy with an Rh+ fetus may be followed by a fatal reaction. Also an Rh- woman of child-bearing age, given Rh+ blood, will be sensitized and will develop anti-Rh agglutinins; if she then has a pregnancy involving an Rh+ fetus the child will develop erythroblastosis, often of the severest type.

To sum up the accumulated facts, it may be stated that Rh incompatibility is of practical importance under the following conditions:

(1) Rh- recipients, men and nonpregnant women, who receive repeated transfusions of Rh+ blood may have intragroup hemolytic transfusion reactions. Such reactions do not occur following the first transfusion; but after a suitable interval for the development of antibodies, further transfusions produce signs of increasing hemolytic reaction with jaundice, anemia and, finally, anuria.

(2) Rh infants born to mothers who have anti-Rh agglutinins may show varying degrees of hemolytic anemia of the newborn, or erythroblastosis fetalis. The severer forms are characterized by late fetal death with congenital hydrops and icterus gravis. In this situation, Rh typing of the mother, father, and child is of diagnostic value, and demonstration of anti-Rh agglutinins in the mother may fix an otherwise questionable diagnosis.

(3) Serious and even fatal hemolytic transfusion reactions may result from the first transfusion in Rh- women who have been sensitized and have developed anti-Rh agglutinins through pregnancies.

(4) The use of Rh+ blood for transfusion of Rh- women, even for the first time, may initiate the formation of anti-Rh agglutinins and produce erythroblastosis of a severe or fatal form in their Rh+ offspring.

For the above reasons, it has become apparent that Rh typing should be carried out in the following persons:

(1) Recipients of whole blood or of resuspended red cells, especially if multiple transfusions are contemplated, in order to avoid giving an Rh- patient Rh+ blood. It is most important to type recipients of multiple transfusions or persons having a history of previous transfusions. Donors and stored blood should also be typed for the Rh agglutinin so that suitable blood is available for Rh- patients.

(2) Any woman whose history suggests the possibility of erythroblastosis—either by one or more stillbirths or infants born with hydrops, jaundice or anemia—before even a first transfusion is given, since a fatal reaction may occur.

(3) Women of child-bearing age before transfusion, since Rh- women given Rh+ blood may be so sensitized that future pregnancies will result in dead or damaged infants.

(4) Babies born with jaundice and anemia, in order that their recovery may be facilitated by transfusion with Rh- blood.

The military services require Rh typing serum even more urgently than do the civilian hospitals, since multiple transfusions are so much commoner in military institutions, and also because obstetric services are expanding in military establishments. It is necessary to have such serum not only for the typing of recipients, but also for the typing of prospective donors, either for Rh- patients or for a donors' list for banked blood for emergency use. The most serious difficulty in this connection has been the relative paucity of available serum. The reasons for this are threefold:

(1) Experimental or animal serum is difficult to produce and gives agglutinations that are unreliable or difficult to read by the average technician.

(2) High-titered serum of human origin occurs chiefly in women recently delivered of erythroblastotic infants and even here it is found in only 1 of 20 such women, 1 in 4000 deliveries.

(3) Such high-titered serum may be extremely specific (70 per cent instead of 87 per cent positive reaction) and therefore may not be useful for general Rh testing. This makes the occurrence of high-titered useful serum about 1 in 6000 deliveries.

For these reasons, other means of increasing the supply of Rh typing material seemed required. It had been noted that low-titered anti-Rh serums were found ten times as frequently as high-titered serums. This material, however, was not safe for general laboratory use because the tests obtained were not clear cut and many negative results occurred with known Rh+ cells. Through the co-operation of the Department of Physical Chemistry of the Harvard Medical School such low-titered serum was concentrated into a globulin fraction yielding good typing results. This opened the possibility of utilizing the more abundant supply of serum containing low-titered Rh agglutinins and thereby possibly meeting the need for Rh typing material.

Accordingly, a project was started under contract from the Committee on Medical Research of the Office of Scientific Research and Development for the collection and preparation of Rh typing serum. During the past six months, meetings have been arranged with obstetricians, pediatricians and clinical pathologists in all the large medical centers, and the facts regarding the need for Rh typing serum have been presented. It has been suggested that they send a few cubic centimeters of blood from any patient known to them who have had a baby with erythroblastosis or possible erythroblastosis (including late fetal death of undiagnosed cause delivered within the last two years. If the serum, by in vitro tests, shows a useful amount of anti-Rh agglutinin, the physician is notified and requested to obtain from the patient 100 to 500 cubic centimeters of blood which is to be shipped promptly. Such material is pooled for concentration of the anti-Rh agglutinin, and a useful typing globulin is produced. Seventy per cent of the resulting serum is set aside for use by the military services, and 30 per cent is credited to the hospital or physician contributing in the enterprise. Such a credit can be drawn on immediately in the form of standard Rh typing serum, so that any hospital or laboratory may have its own material without delay. Special pre-addressed containers and test tubes are being sent to all physicians and hospitals co-operating in this project so that shipment of specimens may be expedited. Also collecting bottles and pre-addressed containers for sending blood serum via air express, collect, are obtainable on request.

Only through such a co-operative enterprise for obtaining large amounts of Rh typing serum does it seem possible to meet the urgent and increasing needs of the military force as more whole blood is being used; also by this means it is hoped to supply the immediate and future demands of obstetric and general hospitals.

All requests for information and for material should be addressed to the Blood Grouping Laboratory, 300 Avenue, Boston 15, Massachusetts.

LOUIS K. DIAM

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